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ACCLIMATISATION TO HIGH ALTITUDES

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A peculiar form of illness, called in English "mountain sickness," has been known for centuries to affect persons who have to pass over or ascend high mountains. The usual symptoms of this illness are nausea, vomiting and headache, with much loss of muscular power, and depression. It has also been known for long that only newcomers are attacked, since inhabitants of high altitudes, or persons visiting them frequently, are "acclimatised."

Until the investigations of Paul Bert, summarised in his well-known book *La pression barométrique*, 1878, the essential cause of mountain sickness was unknown; and even in much more recent times the cause continued to be wholly misunderstood, even by prominent physiologists such as Mosso and Kronecker. Paul Bert's experiments, made partly on animals, and partly on himself in a steel chamber, showed conclusively that whatever other conditions may contribute to the production of mountain sickness, the essential cause is diminution in the partial pressure or concentration of oxygen in the air inspired. At high altitudes this partial pressure is reduced along with the reduction in total atmospheric pressure, though the percentage composition of the air is exactly the same at high altitudes as at sea-level. If the lowering of the oxygen pressure is prevented by adding pure oxygen to the air the lowering of barometric pressure has no effect.

Acclimatisation to high altitudes is thus acclimatisation to an abnormally low partial pressure of oxygen in the air breathed, and the present paper deals with the manner in which the acclimatisation is brought about. The subject is still one of pretty acute controversy among physiologists, though there is now general agreement that Paul Bert's experiments were conclusive as to the real cause of mountain sickness.

There is also now general agreement that the low oxygen pressure

produces its effect owing to the fact that it is insufficient to produce oxygenation of the blood to a normal extent in the lungs, so that the oxygen pressure, or diffusion pressure of oxygen, in the blood passing through the central nervous system is abnormally low. As to how, exactly, the imperfect oxygenation is produced there is controversy, and it is at this point that the present discussion will begin.

The oxygen pressure of the arterial blood of animals has been measured by means of an apparatus introduced in its original form by Pflüger in 1871, and to which he gave the name of the aerotonometer. In this apparatus a relatively large volume of blood from a vein or artery is brought into intimate contact with a limited volume of air of known composition. If the percentage of oxygen or CO_2 in this air rises or falls, the pressure of oxygen or CO_2 must be less or greater than that in the blood; and if we find, for instance, that where, in two experiments in which samples of air containing different percentages of oxygen are introduced into the aerotonometer the percentage of oxygen in the enclosed air rises in one case, and falls in the other, the pressure of oxygen in the blood must be between those in the two. Alternately, we can let blood flow continuously through the aerotonometer till the percentage of oxygen in the contained air becomes steady. If, as Krogh did, we use only a small bubble of air, and analyse it with a gas-burette of almost capillary bore, we can enormously cut down the time required for equilibrium to be produced.

The aerotonometer was progressively improved by Christian Bohr, Fredericq, and Krogh, and has furnished results of the utmost significance, particularly in the hands of Fredericq (1) and A. and M. Krogh (2). One result is that under resting conditions, as nearly normal as possible, the deficiency of oxygen pressure in the arterial blood, as compared with that in the inspired air, is out of proportion lower than corresponds to the rise of CO_2 pressure, after due allowance has been made for the respiratory quotient of the animal. An example from Fredericq will make this clear. In the arterial blood of the animal the pressure of CO_2 was increased to 2.9 per cent, and the pressure of oxygen reduced to 12.8 per cent, or by 8.1 per cent. Allowing for a normal respiratory quotient, we should have expected that if diffusion equilibrium were as complete for oxygen as for CO_2, the oxygen pressure would only have been reduced to about 17 per cent; but it was actually 12.8 per cent, and was thus about 4 per cent lower than it could have been in the alveolar air.

The conclusion which was actually drawn from these results by most

physiologists was that owing to the fact that oxygen is much less soluble than CO_2, the diffusion equilibrium between the blood and the air in the lungs is much less complete in the case of oxygen than that of CO_2, so that the arterial blood is incompletely saturated with the oxygen of the alveolar air, though it is, or may be, in equilibrium with the CO_2. This interpretation seemed to me, however, to present an insuperable difficulty. If the arterial blood were so far from being fully saturated during rest, we should expect that during heavy muscular exertions, with about ten times as much oxygen being absorbed by the lungs, the arterial blood would be so far from full saturation as to be definitely blue in colour, which is certainly not the case. I therefore placed, at the time, a different interpretation on the results. This was that though the blood in the lungs is fully saturated, it loses a little free oxygen before it reaches the aerotonometer or the tissues, owing to the presence in the blood of reducing substances which had not had time to be fully oxidised in the lungs. A very slight oxidation of this sort would be sufficient to account for the fall in oxygen pressure; and there was a considerable amount of apparent evidence, emanating mainly from experiments of Pflüger, that a quite appreciable amount of oxidation of this kind does actually occur in fresh arterial blood.

This interpretation seemed to receive strong confirmation from a very careful series of experiments carried out by Douglas and myself by a quite different method (3). The method depends on the fact, which we had previously verified by exact experiments, that when blood or haemoglobin solution is fully saturated with a gas mixture containing oxygen and carbon monoxide the percentage saturation of the haemoglobin with CO depends, within wide limits, on a constant, multiplied by the ratio of the pressures of CO and oxygen. Thus if we know the pressure of CO, the percentage saturation with CO, and the constant, we obtain at once the partial pressure of the oxygen present. The curve given, for instance, when the results are plotted with the oxygen pressure constant and the CO pressure varied is a sharply defined rectangular hyperbola; and in the whole of physical chemistry no curve has been obtained in which the actual results as plotted against the theoretical ones correspond more sharply. We can thus, if we know the partial pressure of CO when the blood is saturated with it at a known small pressure, determine the mean pressure of oxygen in the arterial blood leaving the lung alveoli by ascertaining, as can easily be done colorimetrically with great accuracy, the percentage saturation of the blood with CO.

Our results showed consistently, and without the smallest doubt, that during rest at ordinary barometric pressure the mean partial pressure of oxygen in blood leaving the aveoli is, as nearly as can be measured, the same as that of the air in the lung alveoli, and not considerably lower, as the aerotonometer results seemed at first to indicate. We thus concluded that either the aerotonometer method or any other method of determining the oxygen pressure or saturation of the blood taken from an artery, is unsuitable for investigating the equilibrium between the oxygen pressure in the alveolar air and that in the arterial blood.

It was with knowledge in this position that the expedition to Pike's Peak, helped by funds from the Royal Society and Yale University, was carried out in 1911 by Yandell Henderson, Douglas, Schneider and myself, together with a supplementary investigation by Miss Fitz Gerald (4); and the manner in which the low atmospheric pressure produces shortage of oxygen in the blood supplied to the tissues was interpreted in accordance with this knowledge. A quite new light was, however, thrown on the whole subject in 1919 by an investigation originating in observations by Meakins, Priestley, and myself (5), on men suffering from the after-effects of gas poisoning and from the group of respiratory and circulatory symptoms known officially as "disordered action of the heart" or "D.A.H." We found that in these men the normal vagus regulation of the depth of breathing was so altered that during exertion, and often even during rest, particularly at night, the depth of breathing is greatly restricted, with corresponding increase in its frequency, and that under these conditions symptoms of shortage of oxygen resulted very easily. We could easily produce symptoms of shortage of oxygen in ourselves by restricting the depth of breathing by one method or another. With the increased rate of breathing which resulted there was an increase in the oxygen percentage of the alveolar air, as obtained in the ordinary way introduced by Priestley and myself; and yet distinct symptoms of oxygen shortage, such as Cheyne-Stokes breathing, were produced, and promptly abolished by increasing the percentage of oxygen in the inspired air.

On consideration of the matter it became evident that the reason for the oxygen shortage of the blood is as follows. The alveolar air as ordinarily obtained is an average of the air in countless alveoli; but the oxygen percentage in different alveoli must vary considerably according as the air-supply is greater or less in proportion to the blood supply. Thus part of the alveoli will contain considerably more oxygen and less

CO_2 than the average, while a corresponding part will contain considerably less oxygen and more CO_2. The mixed arterial blood will reflect the result of this condition. In the case of the CO_2 the effect on the arterial blood will be precisely the same as if all the alveoli contained air of the average composition. This follows from the fact (see fig. 1) that the dissociation curve within the body of the bicarbonate which holds the CO_2 in combination is as nearly as possible a straight line over the interval which comes into question, as shown by the results obtained by Christiansen, Douglas and myself in a well-known investigation published in 1914. In the case of oxygen, on the other hand, the effect on the mixed arterial blood is very different. The

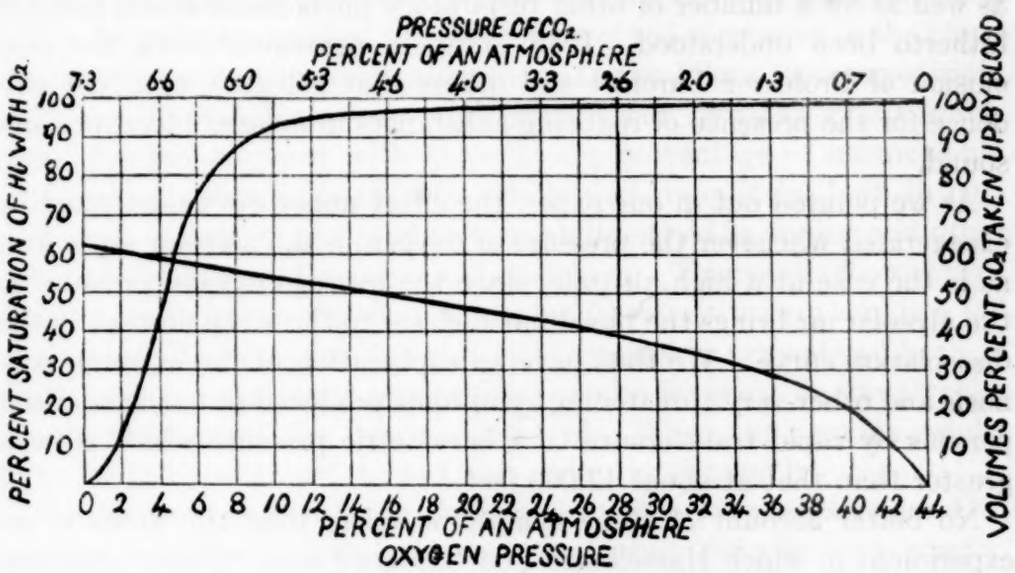
PRESSURE OF CO2
PERCENT OF AN ATMOSPHERE
7·3 6·6 6·0 5·3 4·6 4·0 3·3 2·6 2·0 1·3 0·7 0
PERCENT SATURATION OF Hb WITH O2
100 90 80 70 60 50 40 30 20 10
VOLUMES PERCENT CO2 TAKEN UP BY BLOOD
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
PERCENT OF AN ATMOSPHERE
OXYGEN PRESSURE

Fig. 1. Dissociation curves of blood in the living body for CO_2 and oxygen

dissociation curve of the oxyhaemoglobin in blood has the remarkable doubly inflected form discovered by Christian Bohr. The consequence of this is that blood from alveoli containing the higher percentages of oxygen is hardly at all more highly saturated with oxygen than that from those containing an average percentage; but blood from alveoli containing the lower oxygen percentages is considerably less saturated with oxygen than that from those containing an average percentage. The inevitable result is that the mixed arterial blood is saturated to a very sensibly less extent than corresponds to the average oxygen pressure in the alveolar air.

We thus had in our hands the real explanation of why the oxygen pressure of the arterial blood is always lower than that of the mixed

alveolar air, without any assumption either that there are reducing substances still unoxidised in the blood leaving the lungs, or that there is any appreciable failure whatever in the diffusion equilibration between alveolar air and blood. When the breathing is abnormally shallow, so that considerable parts of the lungs are quite inadequately ventilated, the effect of the unequal ventilation is greatly exaggerated, and we get symptoms, which may be very serious, as, for instance, in the patients we were investigating, or in cases of pneumonia with rapid shallow breathing; but in perfectly normal men or animals, even when the lungs are all the time kept distended with air, these results are still present, and fully account for the low aerotonometer results, as well as for a number of other respiratory phenomena which had not hitherto been understood. I am quite in agreement with the conclusion of Professor Barcroft and others that Pflüger's apparent evidence for the presence of reducing substances in arterial blood was unsound.

As we pointed out in our paper, the effect under discussion must be exaggerated whenever the pressure of oxygen in the alveolar air is low, as is the case at a high altitude, since the average oxygen pressure in the alveolar air brings the blood much closer to the steep descent in the dissociation curve. We thus have an explanation of the extreme cyanosis and other very threatening symptoms produced in unacclimatised persons by rapid transference to a barometric pressure which is even greater than that at about 12,000 feet.

No better account of these symptoms exists than the notes of an experiment in which Hasselbalch and Lindhard went without previous preparation to a pressure of about 515 mm. of mercury, corresponding to about 11,000 feet, in the large steel chamber at Copenhagen (6). Cyanosis was before long produced, and was soon followed by acute symptoms of mountain sickness. At the end of 36 hours the symptoms, including very great cyanosis, precordial pain, and extreme depression, had become so threatening that the life of one of the experimenters seemed to be in danger, and the pressure had to be increased considerably. In subsequent experiments of this series no such serious trouble was experienced at a corresponding pressure. The subjects had become partially acclimatised, just as do airmen and balloonists, or railwaymen who pass over high altitudes. From the analyses of the alveolar air, it appears that the mean alveolar oxygen pressure was about 57 mm. on the second day. Blood saturated with oxygen at that pressure, and at body temperature, would be only very slightly

less red than normal; but we can at once explain the deep cyanosis and other threatening symptoms by the considerations which have been stated.

We now come to the physiolgy of acclimatisation. Previous to the Pike's Peak expedition it had been shown clearly by experiment in the steel chamber at the Lister Institute, London, by Boycott, Ogier Ward and myself, by Ogier Ward on Monte Rosa, and by Douglas on the Peak of Teneriffe, that the alveolar CO_2 pressure gradually falls very markedly at high altitudes, and only returns very slowly to normal afterwards. In other words, the volume, and particularly the depth of breathing are markedly increased, since there is no appreciable change in the production of CO_2 by the body during rest. It had also been known for thirty years that the percentage of red corpuscles in the blood is markedly increased at high altitudes. In the Pike's Peak expedition, including the supplementary work carried out by Miss Fitz Gerald, these changes, together with those in the percentage of haemoglobin in the blood, were followed very closely and completely, both in ourselves and in large numbers of persons acclimatised in mining and other towns of the Rocky Mountains and elsewhere. The results showed very clearly that in persons acclimatised at different altitudes there is a fall in alveolar CO_2 pressure and rise in haemoglobin percentage, both of which are on an average proportional to the lowering in the alveolar oxygen pressure of the persons observed. When the average results were plotted the graph showed this quite unmistakably.

The increase in breathing, indicated by the lowered alveolar CO_2 pressure, raises considerably, and at the higher altitudes very greatly, the alveolar oxygen pressure which would otherwise be present. On the other hand the increased haemoglobin percentage prevents the oxygen pressure in systemic capillaries from falling so low as it otherwise would, with the arterial blood imperfectly saturated. Thus both changes, but particularly the first, afford essential help in diminishing the fall of oxygen pressure in systemic capillaries; and I think that since the Pike's Peak expedition there has been general agreement on this subject.

The marked dependence of the alveolar CO_2 pressure on the alveolar oxygen pressure at high altitudes suggests the question whether, if the alveolar oxygen percentage were raised above normal, the alveolar CO_2 percentage would also rise above normal. To this question we can, I think, reply very decidedly in the negative. It was found by Dautrebande and myself that when pure oxygen is breathed, and partic-

ularly when it is breathed under an extra barometric pressure of one atmosphere, there is a decided fall in alveolar CO_2 pressure (7). In other words, the breathing is increased, the apparent reason being that the circulation in the brain is diminished, thus lowering greatly the oxygen pressure there, but at the same time raising the pressure of CO_2, so that the breathing is increased. But for this circulatory change the increased oxygen pressure in the brain would probably cause rapid pathological effects. In the more lowly organised tissues of the lung, which cannot protect themselves in this way, the increased oxygen pressure soon produces inflammatory changes, as Lorrain Smith discovered. [See addendum page 383.]

With regard to the question whether the haemoglobin continues to fall when the alveolar oxygen percentage is kept above normal, the answer is a very different one. Dr. Argyll Campbell, of the Medical Research Council's Laboratory at Hampstead, authorises me to mention that he has found a very large diminution in the haemoglobin percentage of animals kept for a considerable time in air containing a high percentage of oxygen. The effect of this is to diminish the abnormally high oxygen pressure which would otherwise tend to exist in systemic capillaries.

How is the lowered alveolar CO_2 pressure, and consequent increased breathing, in persons acclimatised at high altitudes brought about? It had been shown first by Galleotti that the amount of acid required to neutralize samples of blood taken at high altitudes is diminished; and at the time of the Pike's Peak expedition this was generally accepted as evidence that the blood at high altitudes is less alkaline than usual. We accepted this as the immediate cause of the increased breathing; but since Ryffel had shown that there is no appreciable excess of lactic acid in the blood of persons exposed to quite low pressures of oxygen, either in laboratories or on Monte Rosa, we suggested that the diminished alkalinity is brought about by the kidneys excreting more alkali than usual, by a special response to the stimulus of want of oxygen. Shortly afterwards Hasselbalch introduced a delicate electrometric method of determining the hydrogen ion concentration of blood, and found, in long steel chamber experiments, that there was in reality no measurable diminution in the hydrogen ion concentration of the blood, in spite of the great diminution in its "titration alkalinity" (8). The diminished titration alkalinity was balanced by the diminished CO_2 pressure, so that the reaction of the blood was sensibly the same.

The real nature of the change in the blood was arrived at independently by Yandell Henderson and Haggard (9), and by Kellas, Kennaway and myself, in 1919 (10). Henderson and Haggard pointed out that since, when a state of acute alkalosis is produced by forced breathing, the so-called "alkali reserve" (which means practically the same thing as the titration alkalinity) of the blood is greatly diminished, the same thing must occur in the blood during the increased breathing caused by want of oxygen, so that it is an alkalosis which leads to the disappearance of alkali from the blood when there is shortage of oxygen. We approached the matter from the same point of view, and found that during the initial stages (corresponding to mountain sickness) of shortage of oxygen the excretion of acid by the kidneys and formation of ammonia is greatly diminished, so that the kidney is reacting quite normally to an alkalosis produced by the increased breathing. The gradual overcoming of this alkalosis by the kidneys is thus part of the process of acclimatisation. The change in the blood consists, therefore, not in the production of a slight acidosis as had hitherto been supposed, but in the compensation of a slight alkalosis by the quite normal adaptive response of diminished excretion of acid and formation of ammonia.

We now come to what may be called the chief present bone of contention in the theory of acclimatisation. The experiments which Douglas and I carried out by the carbon monoxide method, partly on men, and partly on animals, indicated clearly, not only that during rest under normal conditions there is complete diffusion equilibrium between the oxygen in the alveolar air and the blood leaving the alveoli, but also two other things. One was that in animals kept for some time in air containing sufficient carbon monoxide to produce distinct symptoms of oxygen want, the mean oxygen pressure in the blood leaving the alveoli was far higher than in the alveolar air, or even the inspired air. The other was that during fatiguing work with one arm in men there was a similar rise in the oxygen pressure of the blood leaving the alveoli. These results afforded clear evidence that the lungs are capable of actively secreting oxygen inwards from the alveolar air into the blood, just as the kidneys actively transfer materials between the blood and the urine.

The idea that this may be so originated from Ludwig, along with the idea that the oxygen in the lungs helps to turn out the carbon dioxide from the blood. Both ideas were combated vigorously by Pflüger and his pupils. It was finally proved beyond question by Christiansen, Douglas and myself in 1914 that Ludwig was right and Pflüger was

wrong as regards the second idea. The first idea was actively taken up by Christian Bohr, who was one of the greatest of Ludwig's many pupils, and who left behind him, among other pupils, Krogh, Hasselbalch, Lorrain Smith, and myself.

Bohr introduced a type of aerotonometer through which arterial blood could be passed continuously and then returned to the animal. With this apparatus, which involved a very serious interference with the animal's circulation, Bohr thought that he had obtained evidence of active secretion by the lungs. This evidence was, however, far from conclusive; and when Fredericq afterwards performed similar experiments with a somewhat simplified apparatus he showed, first, that it took a far longer time than Bohr had supposed to obtain oxygen equilibrium with arterial blood in the aerotonometer, and secondly that, as already mentioned, when equilibrium is actually obtained (under normal resting conditions) the oxygen pressure of the arterial blood is invariably considerably lower than it can possibly be in the alveoli. Krogh improved the aerotonometer still further, and obtained similar results with a form of the apparatus which was far quicker in its action. He entirely broke away from Bohr on the question of whether the lungs ever secrete oxygen actively. In this I think he made a most serious mistake, though his actual experiments were a model of what experiments ought to be. It is only when secretion is excited by a suitable stimulus that it occurs, and the stimulus was absent in Fredericq's and Krogh's experiments, though it may well have been present occasionally in Bohr's experiments.

Meanwhile the controversy had been further tangled by the publication by Lorrain Smith and myself, of experiments by the carbon monoxide method on ourselves, from which we concluded that even during rest the oxygen pressure of the blood leaving the alveoli is higher than that in the alveolar air. In discussing these results Bohr suggested that the secretion might be due to the abnormal conditions brought about by the fact that in them the blood was kept about 30 per cent saturated with CO. Subsequent experiments showed that not only was this suggestion correct, but through breathing carbon monoxide day after day we had become partially acclimatised to it, in the same manner as was observed during the war in the crews of tanks. The prompt occurrence of oxygen secretion hindered greatly the absorption of CO as soon as the saturation of the blood rose to a certain point. This abnormal condition was carefully avoided in the subsequent experiments already alluded to of Douglas and myself.

It was with knowledge in this position as regards the secretion question that we went to Pike's peak; but we were still quite ignorant of the real reason why the oxygen pressure of the mixed arterial blood is below that of the alveolar air. We were, however, clearly aware that it is quite useless to endeavour to settle the secretion question by either aerotonometer experiments or blood-gas analyses, however accurate, of the arterial blood. The simple method, introduced by Hurter in 1912, for obtaining samples of human arterial blood was, however, not yet known. We knew well that, since the body was reacting continuously in various directions to want of oxygen, an abnormal deficiency of oxygen *must* exist in the blood supplied to the tissues. Before acclimatisation on Pike's Peak this deficiency was so great as to produce very marked blueness of the lips and face. After acclimatisation, however, the visible blueness had disappeared completely. We could easily make unacclimatised blue persons red by giving oxygen; but any difference in colour produced by oxygen after acclimatisation was hardly appreciable, just as at sea-level. It was only after continued heavy exertion that appreciable blueness was visible temporarily in any of us after complete acclimatisation. Blueness in the skin of the face is easily produced at sea-level by the action of cold. On a frosty day outside one can see anywhere typical deep cyanosis of the face; but we took care to avoid the fallacy which might arise in this way. We expected some degree of visible cyanosis, since we knew that in spite of acclimatisation there must be defective oxygenation of the blood; but none could be detected by abnormality of colour during rest. Probably the arterial haemolgobin was at least about 90 per cent saturated with oxygen, as against about 95 per cent at sea-level. With the saturation as low as 85 per cent the bluish colour becomes quite visible in blood.

The experiments on Pike's Peak by the carbon monoxide method gave the clear result that the oxygen pressure of the blood leaving the alveoli was, after acclimatisation, much above that in the alveolar air. The difference disappeared almost entirely when air in which the oxygen pressure had been raised to about that at sea-level was breathed during the experiment. It was also almost absent in an unacclimatised control, whose lips were still blue, though present to the full extent in the same person after acclimatisation, when his lips had assumed a normal colour. We concluded from these experiments, and from all the other available evidence, that oxygen secretion, developing in the course, usually, of two or three days, but often taking longer, is an essential element in acclimatisation.

In which of the tissue elements lying between the blood and alveolar air does this secretion occur? It is known that oxygen secretion against an adverse pressure which may be as much as 100 atmospheres, occurs in the swim-bladder of fishes. The secretion is certainly brought about by cubical epithelial cells in the wall of the swim-bladder, and this fact seemed to render it probable that the alveolar epithelial cells of the lung carry out the secretion of oxygen there. For various reasons, however, it now seems to me more probable that it is the capillary endothelial cells which secrete. This would, at any rate, tend to be a more effective sort of secretion.

The knowledge that the composition of the air in different alveoli varies considerably, and that this influences considerably the oxygen pressure of the mixed arterial blood, renders far more intelligible the need for oxygen secretion. I have already pointed out, from this standpoint, the consequences of diminished oxygen pressure in the inspired air, and of shallow breathing; and the need for oxygen secretion at high altitudes will now be evident enough. But why should oxygen secretion be evoked during muscular work at ordinary atmospheric pressure, and why should it be evoked so easily, while it takes a considerable time to be evoked at high altitudes?

A few years ago I should have been content to say that with the greatly increased oxygen absorption during work the rate at which oxygen can diffuse into the blood would, by itself, be insufficient to saturate the arterial blood to a normal extent with oxygen. This may, in part, be the reason; but my own ideas as to the rate at which oxygen can diffuse into the blood have undergone a very radical change back towards older ideas, formulated by Zuntz. In 1909 Bohr suggested a method for estimating the rate of absorption of oxygen by measuring the rate at which CO is absorbed by the blood when air containing a given percentage of it is breathed; and his calculations for the human lung were based on experiments which I had published as to the proportion of CO which is absorbed when a given percentage of it is breathed. He made the assumption that from the percentage of CO in the expired air we can calculate the percentage in the alveolar air when we know the volume of the "dead space," just as we can calculate the percentage of CO_2 in the alveolar air. Thus when we know the amount of CO which is being absorbed we can calculate the rate at which it is absorbed per millimetre of CO pressure in the alveolar air By making requisite allowances for the greater solubility and slightly less diffusibility of oxygen as compared with CO, we can estimate the

rate of diffusion of oxygen into the blood. This method was further developed and improved by Professor and Dr. Marie Krogh, and in the improved form was generally accepted, by myself among others.

Three or four years ago, I wished to test the method, and set about doing so along with Mr. Ivon Graham, who had devised very delicate methods of estimating CO in air. We found that so far from the percentage of CO in the deep alveolar air being what had been assumed, it was much less. The alveolar air was thus very far from being constant in composition, and there was very little CO in the deep alveoli. Thus the method in the forms hitherto described is unreliable, and the real rate of diffusion is greater than what had been concluded. The rate of diffusion could thus have but little to do with the need for secretion of oxygen in work at ordinary atmospheric pressure. Krogh himself had drawn a similar conclusion from his own experiments and those of Madame Krogh, and though their method was actually unreliable, I am glad to be now in agreement with them on this point. The variable composition of different strata of the alveolar air when an easily soluble gas is being absorbed has also been pointed out recently by Yandell Henderson and Haggard.

That shortage of oxygen occurs readily in the blood of persons not in physical training is shown strikingly by the good effects of enriching the inspired air with oxygen. The main reason for the need of oxygen secretion during muscular work seems to be that during muscular exertion the venous blood is far more venous than during rest. The experiments of Christiansen, Douglas and myself on the dissociation curve of the CO_2 in human blood within the body placed in our hands a perfectly reliable method of measuring the rate of blood-flow through the lungs in man; and this method showed at once that the rate of blood-flow during rest is very great, with the oxygen-pressure of the mixed venous blood correspondingly high. The later experiments with this method (11) showed that during work the blood-flow does not increase in anything like the same proportion as the general metabolism, with the result that the oxygen pressure of the mixed venous blood (which now contains a very large proportion of blood from muscles) is far lower. The lung ventilation increases almost in proportion to the general metabolism, but in the less amply ventilated alveoli the oxygen pressure can fall much lower than during rest. Hence the effect of the varying alveolar oxygen percentage on the oxygenation of the mixed arterial blood would be much more serious than during rest, but for active secretion. The stimulus to this secretion must,

apparently, be some substance produced in the tissues, and particularly in active muscles.

Strong confirmation of the latter conclusion is afforded by the fact that in experiments on unacclimatised persons at low pressure in steel chambers the symptoms and the colour of the lips are greatly improved by moderate work, as with a hand ergometer. This was specially noted recently by Schneider and Clarke (12), and was also mentioned many years ago by Loewy, as stated in my book, *Respiration* (p. 236). The fact would be very difficult to interpret except on the secretion theory.

Perhaps the main opponent of the secretion theory is Professor Barcroft. In his recently published book on *The Respiratory Function of the Blood* (13), published a few months ago, he has stated his reasons for concluding that secretion of oxygen plays no part in acclimatisation, and he offers very candid criticisms of our reasoning on this subject. Though no one appreciates more fully than I do his solid contributions to physiology, I must be equally candid in my criticisms of his own reasoning and experiments.

His main reason for rejecting the secretion theory is that he has never found that the oxygen pressure of the mixed arterial blood is higher than that of the mixed alveolar air. He cites an experiment on himself in 1920, when he remained for several days in a falling percentage of oxygen, and at the end obtained a sample of his own arterial blood, which gave an oxygen pressure distinctly lower than what he believed to be that of his alveolar air. In this experiment he became extremely ill and his body temperature had risen. It is perfectly clear that he was not anything like acclimatised, so that the experiment was a failure, so far as any testing of the secretion theory was concerned. From what has been said above it follows also that his method of testing the secretion theory was very unsatisfactory. In my book on *Respiration* at pages 253–255 I have fully criticised the details of this experiment, and I also give the results of two similar experiments on myself, one of which, made in 1916, was completely successful (p. 241), while in the other the acclimatisation failed in the same way as in Barcroft's experiment, or in the experiment of Hasselbalch and Lindhard, already referred to.

Barcroft's main reliance, however, is on the results of the expedition made in 1922 by him and his party to Cerro de Pasco in Peru, at a height (14,200 feet) almost identical with that of Pike's Peak (14,100 feet) (14). In commenting on these results I am in a difficulty, which

Barcroft passes over completely in his book. He found that the dissociation curves of the oxyhaemoglobin in the blood, not only of natives of the place, but also of the members of the expedition, was in every case very markedly altered in such a way that the blood would, at a given pressure of oxygen, and the existing alveolar pressure of CO_2, take up much more oxygen from air with low pressures of oxygen than normal blood. But this observation is directly contradictory to those made previously by Barcroft himself on the Peak of Teneriffe and Monte Rosa, and the confirmatory ones made by Douglas and myself on Pike's Peak. These latter observations were made with very particular care, as we wished to leave not the smallest room for doubt on the subject. We were also particularly familiar with the most accurate methods of determination, and used them.

Now Nature does not behave in the haphazard fashion which might at first be suggested by this difference. In other words either the results of the three previous expeditions seem to have been wrong, or those of the Peru expedition. I naturally prefer the latter alternative, and would suggest as one possible explanation that a thermometer used in measuring the temperature of the bath in which the saturations were made had, during the voyage, got a small bubble of gas into the bulb, so that the reading was too high. It is easy for this particular defect to pass unnoticed, and it would at once account for the anomalous results. In any case it does not seem possible, without further confirmation, to accept either the dissociation curves or the inferences based on them, as correct. I must also point out that even if the alteration did exist it would in no way help to explain the fact of acclimatisation; for the more tightly the oxygen combines with the haemoglobin in the lungs the more tightly will it hold on in the tissues, so that they will be just as short of oxygen.

Various direct determinations are also given in the Report of the Peru Expedition of the oxygen pressures of arterial blood. These are made by an aerotonometer method based on that of Krogh, but differing from it in essential points. The determinations by it for normal arterial blood at ordinary atmospheric pressure give as a result that the oxygen pressure of arterial blood is identical with that of the alveolar air. This method seems to me quite unreliable for arterial blood, owing to the time given for equilibration between the oxygen pressures of the blood and the bubble of alveolar air in the aerotonometer being insufficient. For evident reasons such equilibration occurs rapidly with venous blood, but very slowly with arterial blood, as Fredericq proved.

Barcroft's results for arterial blood with this method are not only inconsistent with those of Fredericq and Krogh, already referred to, but also with the results of the careful experiments by Meakins and Davies on the degree of unsaturation of normal human arterial blood. These experiments indicate that, just as in the case of the normal animals investigated by Krogh, the arterial oxygen pressure of the mixed arterial blood is about 15 mm. below that of the alveolar air. For these reasons I think that we must disregard Barcroft's aerotonometer results. He had never tested the method with arterial blood, and he seems to have fallen into the same error as Fredericq pointed out in the case of Bohr's aerotonometer experiments.

There remain certain solid and reliable observations bearing on the question of oxygen secretion. The first of these is the fact that natives of the place, and at least one other person who had been long resident, had a quite evident bluish colour of the lips etc., which was turned to a normal colour on administration of oxygen or on transference of the person to a lower altitude. On analysis, the haemoglobin in the arterial blood of three of these natives was found to be only about 83.5 per cent saturated with oxygen. Yet they were thoroughly acclimatised in the sense that they could live a healthy life, and were capable of considerably greater muscular exertion than newly acclimatised Europeans.

It is well known that persons with chronic emphysema or certain chronic heart affections may be leading a fairly normal existence though their lips and skin are constantly more or less blue, with the arterial blood evidently unsaturated to a considerable extent. These cases show distinctly that acclimatisation to a considerably lowered arterial oxygen pressure may be acquired in time, and I have referred to this subject in my book on *Respiration* at page 131. It may very well be that in the brain and other parts where a high oxygen pressure is normally required the capillary walls come to be capable of actively secreting oxygen outwards, though on this point there is no evidence at present. Whatever the nature of the adaptation, the observations on the natives seem to me to show that they have acquired it to a considerable extent. To what degree they also secrete oxygen could only be decided by means of the carbon monoxide method. The fact that they are capable of greater and much more sustained physical exertion than Europeans living at the same altitude indicates also that they are adapted to a lower arterial oxygen pressure.

A considerable number of analyses are given showing the percentage

saturations with oxygen of the haemoglobin in the arterial blood of members of the expedition and other Europeans. These are, with one exception (that of Harrop, for whom only a single analysis exists), very much what would be expected from the observations made in the Pike's Peak Expedition. In the case of Meakins, for instance, the saturation found was 83 per cent on the day after his arrival, and 91 per cent a fortnight later (three analyses), by which time he would be pretty fully acclimatised. On the same day the oxygen saturation of his blood went down to 79 per cent during "work." On Pike's Peak it needed fairly hard and continued work to produce blueness of the lips. In the case of Redfield, who also did work while the sample was taken, the work was evidently insufficient to produce blueness, as the oxygen saturation was 90.5 per cent (three analyses). Unfortunately no data are given as to the degree of acclimatisation which had been reached by the subjects; and one can only guess at this from the dates given, which are not always consistent.

If we admit that in this expedition the dissociation curves of the oxyhaemoglobin were all altered in the manner described in the Report, it follows that the arterial saturations were in no case greater, and in most cases less, than corresponds to the mean oxygen pressure of the alveolar air. If, on the other hand, we believe, as I do, that the curves were practically unaltered, as was found to be the case for every individual investigated in the three previous expeditions, then the oxygen pressures in the arterial blood were mostly above those of the alveolar air, so that even by Barcroft's own measure the lungs were actively secreting oxygen. For the reasons stated above, and previously stated again and again in our published papers, Barcroft's measure of secretion is, however, no measure at all, and not even a satisfactory qualitative test.

I think that Professor Barcroft has failed to realise the quantitative aspects of the evidence bearing on secretion. He has also been led into what appears to me a most amazing misrepresentation of my own views on the subject. In his recently published book that misrepresentation is ludicrous. I have never, either recently or at any time, held the essentially ridiculous view which he attributes to me, that after acclimatisation the blood taken from an artery has an oxygen pressure as high as at sea-level. This will be evident enough from the summary account in this paper, or from the clear statement at page 373 of my book. I must add that I am particularly sorry that he has specifically countenanced the old view that when the arterial blood of

a pneumonia patient is only about 80 per cent saturated with oxygen, this is not a condition calling urgently for active treatment. A pneumonia case is not comparable to a case of congenital *morbus coeruleus*, or of chronic emphysema, or to that of a native of Cerro de Pasco.

I now turn to the observations accumulated recently during the two splendid attempts to reach the summit of Mount Everest at 29,000 feet, or a barometric pressure of about 270 mm. (14). As set forth very fully and clearly in the Pike's Peak Report, the only evidence then existing as to the extent to which acclimatisation could be carried was derived from the records of mountaineers in the Himalaya; and the most striking evidence was that afforded by the experiences of the well-equipped expedition of the Duke of the Abbruzzi in 1909. The expedition reached a height of 24,600 feet without any mountain sickness in the climbing party; and this fact led to the extraordinary conclusion, in the Report of the Expedition, that mountain sickness is not due to want of oxygen or diminished atmospheric pressure, but to fatigue caused by lack of proper physical training. Such a conclusion was of course quite inconsistent with existing knowledge; but that both good physical training and previous exposure to low atmospheric pressures have a considerable influence in preventing mountain sickness is well known to both mountaineers and airmen. The oxygen secretion theory furnishes at once an explanation of these facts. Secretion, as we have seen, does not exist during rest, but is evoked by muscular exertion, and much less readily and more slowly by want of oxygen in the arterial blood unless this want is very great, as in severe CO poisoning. With practice it is evoked more readily and to a greater extent; and this condition is an essential part of physical training, and acclimatisation to the effects of high altitudes or CO poisoning. The latter fact was brought out in the clearest manner by the experiments of Kellas, Kennaway and myself in steel chambers; but, as we pointed out, the degree of acclimatisation obtainable in this way was limited by the fact that the breathing was not increased as it would have been in persons acclimatised by continuous residence at a high altitude. We were only in the chamber for a few hours each day at increasingly low pressures.

The new physiological facts elicited by the Mount Everest expeditions are of the most striking character. In the first place it was shown that acclimatisation sufficient to prevent any symptom of mountain sickness could be obained at a height of even 27,000 feet, and probably higher. The experiences of Colonel Norton, Doctor Somervell and Mr. Odell on this point are conclusive. Not only had they no mountain

sickness on staying over a night at 27,000 feet, but they could sleep well, and were quite comfortable during rest, in so far as the extreme privations suffered render it possible to speak of comfort. To an unacclimatised person a stay of any duration at a height of 27,000 feet means absolutely certain death within a very short time. Even at a barometric pressure corresponding to 21,000 feet my son, Mr. J. B. S. Haldane, who acted as the unacclimatised control in the acclimatisation experiments of Kellas, Kennaway and myself, was reduced at the end of two hours to a condition of failing consciousness and respiration, so that it became urgently necessary to release him from the chamber; and I have already referred more than once to the effects of a much more prolonged stay at far less low pressures, with unacclimatised subjects. At heights above about 12,000 feet death from mountain sickness may quite well occur in persons who are completely unacclimatised and in bad physical training.

We found that at 25,000 feet, in our partially acclimatised condition, the addition of even a small proportion of oxygen (one litre, measured at atmospheric pressure, a minute) had an enormous effect in facilitating heavy muscular exertion, which, indeed, was quite impossible without the oxygen. We therefore anticipated a similar good effect in the Mount Everest Expedition. These anticipations were, however, only very partially fulfilled. In certain cases there was distinct benefit from the oxygen; but in those members of the expedition who had become acclimatised at the highest altitudes no distinct benefit could be observed. What is the explanation of this? The explanation now seems evident enough, though before the expedition I never anticipated the actual effects.

In men who are thoroughly acclimatised there is not only, as we have seen, a great increase in oxygen secretion, but also a great fall in the pressure of CO_2 in the alveolar air, and consequently a great increase in the volume of air breathed. This increase causes little or no inconvenience during rest, but limits more and more the amount of muscular work which is possible without intolerable panting. Hence the greater the altitude at which a man is acclimatised the less muscular work can he do, since his power of panting is limited. Even on Pike's Peak the rate at which we could climb was greatly limited by the panting which the exertion produced. The panting became absolutely intolerable if we endeavoured to go faster, though sometimes no evident blueness of the lips was produced. At the higher camps on Mount Everest the alveolar CO_2 pressure was evidently so much reduced that,

quite apart from any extra shortage of oxygen at the time, the rate of climbing work possible was cut down to a fraction of that at sea-level. Hence the relief produced by a supply of oxygen was so small as to be hardly worth the extra trouble and extra weight carried, at any rate when two or more of the cylinders were carried. When, however, the wearer was only acclimatised at a lower level, so that the breathing was not so much increased by the acclimatisation, a considerable net advantage was obtained from the oxygen apparatus.

If we judged simply by the graph published by the Pike's Peak Expedition, the alveolar CO_2 pressure at 27,000 feet would only be reduced to about 19 mm. With no further reduction than this a considerable rate of climbing work would still be possible, and particularly if sufficient oxygen were supplied, since, as was clearly and quantitatively shown by the Pike's Peak observations, part of the increased breathing with hard work is directly due to want of oxygen. I think, however, that there can be little doubt, from the actual experience with oxygen apparatus, that the alveolar CO_2 pressure during acclimatisation runs down more rapidly at very great altitudes than the graph indicates, and was probably not more than about 12 mm., with a correspondingly higher alveolar oxygen pressure of about 35 mm., at 27,000 feet.

Owing to the death in the first Everest expedition of Doctor Kellas, who was fully equipped for physiological observations, no reliable samples of alveolar air were obtained at the higher altitudes by the expeditions,[1] and there were no observations of the colour of the lips, etc., apart from changes of colour which could be attributed to cold. Nevertheless the symptoms described, and particularly the extreme panting on exertion and absence of mountain sickness, leave little doubt as to the actual physiological conditions. The increase in the breathing had, as it were, almost defeated its own objects by rendering the exertion of climbing impossible except at an extremely slow pace, quite apart from any immediate effects of want of oxygen. The acclimatisation was, however, extraordinarily complete up to 27,000 feet; and this and the nature of the further climb to the summit, left no doubt that if only favourable conditions of weather existed the summit could be reached without the use of oxygen.

[1] Doctor Somervell obtained, and analysed at a later time, a number of alveolar air samples collected in a small rubber bag at a height of 23,000 feet (Journ. Physiol., 1925, lx, 282); but the results were quite unreliable, owing to the fact, of which he was unfortunately ignorant, that rubber, as was shown by Graham, is easily permeable by CO_2, and is more permeable to oxygen than nitrogen. In a small bag this causes great error unless the samples are analyzed at once.

If it were possible to furnish with sufficient oxygen a climber acclimatised at, say, 23,000 feet, he would certainly be able to employ sufficient exertion to climb the rest of the way at a fair, though very slow, pace; and relays of oxygen, carried by men breathing air, could, apparently, be provided for him up to 27,000 feet. He would, however, be in some danger if the oxygen apparatus broke down. It is curious to reflect that a climber who was totally unacclimatised, but was in good training, and provided all the way with oxygen, could ascend the whole way just as rapidly as if he were climbing near sea-level, or possibly even more rapidly.

To account for the acclimatisation on Mount Everest without the assumption of active secretion of oxygen inwards by the lungs appears to me to be an absolutely hopeless task. The secretion theory, in conjunction with the other known factors in acclimatisation, accounts for all the known facts satisfactorily; but apart from the secretion theory these facts are an unintelligible chaos. The direct evidence for the secretion theory seems to me to be also quite clear.

It is only by quantitative observations and experiments that we can approach the physiological problem of acclimatisation; and from the quantitative side it seems impossible to avoid the conclusion that in persons acclimatised at high altitudes the lungs are actively secreting oxygen, just as Ludwig originally suspected that they are capable of doing. Both of the new suggestions which he made as regards the specific occurrences in the lungs have thus been verified, while the conclusions of Paul Bert as to the root cause of mountain sickness and the other physiological troubles associated with high altitudes stand absolutely intact.

ADDENDUM TO PAGE 370. The fact that the circulation through the brain is diminished when pure oxygen is breathed has quite recently been demonstrated by J. Tivel, who observed, in several patients who had been trephined, that the exposed grey matter became paler when pure oxygen was breathed. (C. R. de la Soc. de Biol., March 18, 1927.)

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PHLORHIZIN DIABETES

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From the discovery of phlorhizin by de Konick (112) in 1835, until the publication by v. Mering (138), fifty years later, of his first researches concerning the physiological effects of the substance, the glycosuric effect of phlorhizin apparently escaped observation. After the drug was very early tested and rejected as a remedy for malaria, the meagre phlorhizin literature of this first period continues to be concerned mainly with attempts to find clinical applications.

The productive era of phlorhizin experimentation dates from the fundamental observation by v. Mering that phlorhizin renders animals glycosuric. Physiologists were quick to appreciate that a prolific new resource in the study of metabolic processes had been made available. In the succeeding twenty-five years were constructed many of the concepts of physiological processes which today are regarded as fundamental. Lusk (124) who, more than any other, was responsible for standardizing and developing to a quantitative basis the technique of phlorhizin experiments, has carefully reviewed the very abundant phlorhizin literature of this period.

It is the purpose of the present review to summarize briefly the further developments in phlorhizin research during the last fifteen years. The discovery, in the later years of this last period, of insulin has supplied a new agency and a fresh idea by which to measure and check the older ideas concerning the mechanism of phlorhizin action. It is, of course, an obvious proposition that an accurate understanding of the mechanism of phlorhizin action is essential to the final validity of conclusions concerning metabolic processes occurring in the phlorhizinized organism. The contributions to the whole subject with which this paper is concerned may be classified, very generally, as those which have sought to elucidate the mechanism of the action of phlorhizin; and those which, relying upon some theory of this mechanism, have employed the phlorhizinized animal as a subject for the study of various

phases of the intermediary metabolism. It is in this order that the work will be presented.

I. THE MECHANISM OF PHLORHIZIN ACTION. *a. The action of phlorhizin upon the kidney:* v. Mering (139) was clearly of the opinion that phlorhizin glycosuria is caused by a specific effect of the glucoside on the kidneys. His finding of a characteristic hypoglycemia in phlorhizinized animals led him to propose the "Elimination Theory," and to distinguish between diabetes, where the organism has lost the capacity to oxidize carbohydrate, and glycosuria, where the organism is unable to hold back the sugar in normal manner. In a classical demonstration Zuntz (223) proved a direct effect of phlorhizin upon the renal tissue, a fact which has been amply confirmed. However, this early emphasis upon the renal site of phlorhizin action for a time diverted attention from the possibility of a more generalized effect upon the body tissues.

Whether phlorhizin so affects the kidney as merely to increase its permeability to glucose circulating free in the blood, or whether the kidney is stimulated to the active production of sugar, is an issue that is still debated. Lépine and Boulud (114), who have consistently supported the view of sugar production by the phlorhizinized kidney, have described the following experiment as evidence that the excreted sugar is set free from the "sucre virtuel" in the renal capillaries: Catheters were introduced into the ureters of dogs. A pressure was exerted, on one side with physiological sodium chloride solution, and on the other side with a slightly alkaline solution of sodium chloride containing phlorhizin. Pressure was maintained until several cubic centimeters of the solutions had been absorbed. After a very short, initially high, sugar excretion on the phlorhizin side, the further excretion of sugar on this side was less than on the sodium chloride side. The authors believe that the renal epithelium is thus damaged by phlorhizin so that the sugar excretion is diminished, whereas on the less damaged side the phlorhizin circulating in the blood stimulates the excretion of sugar. Allen (3) came to the conclusion that a simple (active or passive) increase of renal permeability seems less probable than the hypothesis that the kidney derives the sugar from some larger molecule or complex. All glycosurias known to depend upon passage of blood sugar into the urine are, according to Allen, increased by diuresis; phlorhizin glycosuria stands out in contrast. More recently, Brugsch, Exten and Horsters (21) have claimed that phlorhizin diabetes differs from pancreatic diabetes in that in the former sugar is primarily formed in the kidneys, while in the latter the liver plays the major part.

The fact that maximally phlorhizinized dogs show in the urine an average D:N ratio of about 3.6, whereas depancreatized dogs and most other species of animals when phlorhizinized yield a D:N quotient of about 2.8, has supported the suggestion of a colloid or some other form of combination of dextrose, which is split only by the kidney showing the higher ratio, and in other cases presumably is utilized (cf. Lusk, 124).

If sugar is, in fact, synthesized in the kidney, or is there set free from some form of combination which is not measured in the estimation of the blood sugar, it would be expected that a higher concentration of sugar should be found in the renal vein than in the general circulation. Levene (115) was the first to report that the sugar content of the renal venous blood is more than that of the renal arteries. Reinvestigating the question with more exact methods of blood sugar analysis, Schenk (188) and Nash (146) failed to confirm Levene's observations. On the contrary, Nash found in experiments on phlorhizinized dogs significant losses in the sugar concentration of blood passing the kidney in those cases where the animals retained an appreciable renal function under the anesthesia employed for collection of blood from the kidney vein. There was a direct proportion between the sugar excreted in the urine and the loss from the blood, and it appeared that the total loss from the blood was probably sufficient to account for the whole amount excreted. Even where the excretory power of the kidney was largely abolished there was no increase in the sugar content of the venous blood of the kidney.

Working with the heart-lung-kidney preparation, de Boer and Verney (19) found that the amount of sugar which appeared in the urine after addition of phlorhizin to the circulating blood could be completely accounted for by the fall in blood sugar over the same period of time.

Even after maximal phlorhizin effect in rabbits Mayrs (135) finds that the kidneys are still able to concentrate sulphate better than dextrose; hence phlorhizin does not completely prevent the reabsorption of dextrose in the kidney.

Shioya (193) has suggested that the permeability of the kidneys to glucose is increased by an unknown metabolite resulting from the augmented metabolism.

Junkersdorf (107) holds that the characteristic hypoglycemia of the phlorhizinized animal is attributable not entirely to renal cause, but is based upon a disturbance in the blood sugar regulating function of the liver.

b. The action of phlorhizin upon glands other than the kidney: Hyrayama (98) could find no significant differences in the sugar content of saliva, pancreatic juice, bile, the secretion of the intestine, or gastric juice, before and after phlorhizin administration. Pearce (156) investigated the reducing power of pancreatic, gastric, and salivary secretions in normal and phlorhizinized dogs. Whereas no appreciable amount of reducing substance was found in the juices of normal dogs, in phlorhizinized dogs the gastric and pancreatic juices, and sometimes the salivary secretion, contained a reducing substance in very small amount. Smyth and Whipple (196) report that phlorhizin has no influence upon the bile salt output in bile fistula dogs. Nakazawa (145) studied the absorption of solutions from isolated segments of the intestine in narcotized rabbits, and found that the absorption of glucose was strongly repressed by phlorhizin, whereas there was no effect upon the absorption of water, sodium chloride, glycocoll, or fatty acids.

c. The effects of phlorhizin upon the carbohydrate metabolism: The question of major importance in the whole problem of phlorhizin diabetes is whether the condition represents a complete carbohydrate intolerance. Is the pathway of carbohydrate oxidation in the "maximally" phlorhizinized animal definitely and irreversibly blocked? Long ago Cremer (39) raised the question whether there is, in fact, a total phlorhizin diabetes in the sense that the influence of phlorhizin upon the organism is such that dextrose cannot be burned. It is quite clear that the final interpretation of much of the important work which has been accomplished upon the intermediary metabolism of the energy food substances involves a definite appreciation of the quantitative limitations of the carbohydrate process.

The tests which have been relied upon to decide the degree of effect of phlorhizin upon the oxidative metabolism of carbohydrate are mainly two: the recovery in the urine of dextrose after the administration of sugar or substances theoretically anticipated to yield a definite amount of dextrose; and examination of the respiratory exchange. It must be admitted at once, however, that no unanimity of opinion has been arrived at.

A very positive view has been taken by Allen (3) that phlorhizin effects no intrinsic impairment of utilization of carbohydrate. Phlorhizin, according to Allen, compels the excretion of more or less dextrose through the kidneys; but when this demand is fully satisfied, the phlorhizinized animal is able to utilize sugar just as readily as any other animal.

Galambos and Schill (75) have claimed that phlorhizin may entirely abolish, or only diminish, the capacity to burn sugar, the degree of effect depending upon the amount of phlorhizin administered and the time elapsed between the use of phlorhizin and the subsequent introduction of dextrose.

It is not proposed, however, to cite here all who have ventured an opinion upon this subject. The significant consideration is that the available evidence could have been so variously interpreted.

1. Recovery of dextrose: Reilly, Nolan and Lusk (158) gave to a maximally phlorhizinized dog 24 grams of dextrose and recovered 94 per cent of it in the urine as extra sugar. This original observation has since been repeated many times by various workers, with various quantities of sugar, and with essentially similar results. Provided the amount of sugar administered is within reasonable physiological limits, generally between 90 and 100 per cent of it is recovered in the urine. When excessively large quantities of sugar are employed, there is some indication that its recovery is relatively less complete; but this condition has not been sufficiently studied.

Ringer (161) found that 69.5 grams, or 93 per cent, of 75 grams of dextrose fed were eliminated unburnt. Nash and Benedict (149) administered 30 grams of dextrose to a phlorhizinized dog and obtained 95.5 per cent of it in the urine. Nash (148) has reported recoveries as high as 99.2 and 99.5 per cent when 30 to 60 gram doses of dextrose were given to phlorhizinized dogs; in one case 107 per cent was recovered when 25 grams were given. Deuel and Chambers (49) fed various sugars in 16 gram doses to phlorhizinized dogs and obtained 105 and 107 per cent recoveries in the case of dextrose, 93 and 94 per cent after levulose, and 88 per cent after galactose.

A multitude of comparable results might be cited. Occasionally, pronounced, quantitative exceptions to the rule are found, as, for example, by Nash (148) and Sansum and Woodyatt (182). Such exceptions, while sometimes apparently inexplicable, are more frequently attributable to the physical condition of the animal; and, in smaller degree, to the unavoidably *approximate* accuracy of the assumptions involved in the calculation of "extra" sugar in all phlorhizin experiments.

That the essential failure of the oxidative carbohydrate process in the phlorhizinized animal is not due to a tissue hypoglycemia was shown by Nash and Benedict (149) who gave to phlorhizinized dogs 30 gram doses of dextrose by stomach, and observed a hyperglycemia up to three

times the normal blood sugar concentration, which endured for 6 hours or longer. Despite a concentration of sugar within the organism well above the normal level no sugar was burned, as judged by the "quantitative" recovery of the sugar in the urine. These authors take the view, contrary to Allen, that phlorhizin does produce an intrinsic impairment of utilization of sugar by the tissues. They suggest, tentatively, that phlorhizin blockades the sugar-burning mechanism of the cell in much the same sense that carbon monoxide blocks the oxygen-combining capacity of hemoglobin; not only does phlorhizin affect the kidney tissue, but all other metabolizing tissues as well, and probably in much the same manner.

A hyperglycemia following the administration of sugar to phlorhizinized dogs has also been reported by Hornemann (97) and Csonka (42), who found that the same quantities of sugar in normal dogs were without comparable effect upon the blood sugar values. These important observations merit very careful consideration by those who would restrict the mechanism of phlorhizin action to a renal effect.

Csonka observed further, after the ligation of the renal vessels and ureters of a phlorhizinized dog, and the subsequent oral administration of 50 grams of dextrose, an increase in the blood sugar from 0.058 to 0.290 per cent within 2 hours. The corresponding blood sugar values in a non-phlorhizinized dog under otherwise duplicate conditions were 0.075 and 0.076 per cent, respectively. Underhill (207) found a significant hyperglycemia in completely phlorhizinized dogs, after ligation of the renal structures, as well as in phlorhizinized rabbits whose kidney function had been abolished through subcutaneous administration of tartrate. He viewed this evidence as corroborative of v. Mering's theory and indicative also of an action exerted by phlorhizin upon other structures than the kidney. Hetényi (95) claims that in subjects whose kidneys are so diseased that phlorhizin does not cause glycosuria there is a definite hyperglycemia after giving the phlorhizin. Such findings are in striking contrast to the earlier observations of Minkowski (140), Schabad (187), Levene (115) and Lewandowsky (116), none of whom was able to detect an increase in the blood sugar following ablation of the kidney function. More recently Epstein and Baehr (57) failed to find an increase above the normal value of blood sugar in nephrectomized, phlorhizinized cats. These authors believe that phlorhizin stimulates the accumulation of glycogen in the liver, and in the absence of the kidneys this effect of the drug becomes apparent.

A personal communication from Dr. H. J. Deuel, Jr., reports a new,

and as yet unpublished study of the blood sugar in nephrectomized and phlorhizinized dogs, which is being carried out with the collaboration of Dr. H. E. C. Wilson and Dr. A. T. Milhorat in the laboratory of Prof. Graham Lusk (cf. page 403). In these experiments the administration of phlorhizin did not intensify the slight hyperglycemia which existed after extirpation of the kidneys. There was a considerable rise in the blood sugar only just before death, though the majority of the animals survived the operation from four to six days. The effect noted by Underhill (above) is attributed to the fact that his animals lived only about 12 hours.

The question of the course of the blood sugar in phlorhizinized animals with renal impairment is of sufficient interest to justify further confirmation. As Ringer (161) has said: "If the kidneys were not the only seat of attack of the phlorhizin, and if phlorhizin *per se* had any influence on the sugar burning capacity of the cells of the body, nephrectomy should have been followed by a rise in the glucose concentration of the blood . . . . ." Such experiments, however, should take account of the now established fact that hyperglycemia in phlorhizinized animals may lead to extensive synthesis of glycogen and its deposition in liver and muscle, and conversely the formation of glycogen may keep down the hyperglycemia until the glycogen stores have become well filled.

Evidence of an entirely different character bearing upon the question of a direct inhibition exerted by phlorhizin has been given by Gottschalk (79). When a buffered liver mince was kept at 40°C. for 24 hours, there was a production of acetaldehyde. The addition of phlorhizin to such a mince prevented formation of the aldehyde; phlorhizin does not destroy acetaldehyde.

Sweet and Ringer (200) performed Eck's fistula operation on five dogs. The dogs were kept from one week to two months, when phlorhizin was administered. The glycosuria that followed resembled in every detail the phlorhizin glycosuria of non-operated dogs. The power of gluconeogenesis, as measured by the extra sugar eliminated after the subcutaneous injection of glycocoll, was not diminished by the operation. These results contradict Rosenfeld (177) who found after shunting the portal blood into the inferior vena cava, in a dog, that an injection of phlorhizin produced no glycosuria. Foster (64), however, confirms that phlorhizin induces glycosuria in Eck's fistula dogs. Burghold (23) has called attention to the readiness with which such animals develop a toxic condition which appears to be associated with the extreme impoverishment of carbohydrate.

Austin and Ringer (10) found that removal of the spleen was without effect upon the sugar elimination, D:N quotient, and degree of acidosis in a phlorhizinized dog. This finding bears upon the question whether the spleen, as has been maintained, possesses an activator for the enzyme which causes a condensation of the glucose molecule in muscle, liver, pancreas, and lung (cf. P. A. Levene and G. M. Meyer: Journ. Biol. Chem., 1912, xi, 356).

2. Glycogen formation: It is definitely proved that phlorhizin administration alone will not completely deglycogenize an animal. While the glycogen content of the liver is rapidly reduced to a fraction of its normal value, and the muscle glycogen is also rapidly and considerably reduced, nevertheless glycogen is still to be found, at least in the muscle, even after prolonged starvation of the maximally phlorhizinized animal. Ringer, Dubin and Frankel (169) in a very extensive series of experiments on fasting phlorhizinized dogs obtained the following results: At the end of two days of glycosuria the average glycogen content of the muscle of 13 dogs was 0.482 per cent; at the end of the third day the muscles of 11 animals contained an average of 0.306 per cent of glycogen; at the end of the fourth day the average value in 12 animals was 0.228 per cent; at the end of the fifth day 7 animals showed an average muscle glycogen of 0.155 per cent; and at the end of the seventh day 2 animals showed 0.124 and 0.151 per cent of glycogen in the muscle. The authors term this glycogen which is so tenaciously held in spite of the tremendous demand for it, "residual glycogen," and infer that it must have a different significance in the cell economy from the ordinary mobile glycogen that moves in and out of the cell. Woodyatt (219), however, could find no glycogen in the liver or muscle of a phlorhizinized dog with a D:N ratio of 3.73.

Lusk (123) inferred that exposure of phlorhizinized animals to cold or mechanical exercise would completely remove glycogen from the tissues, since subsequent deglycogenizing procedures were without effect upon the D:N ratios of the urine. Ringer (159) found that "extra sugar" excretion in phlorhizinized animals followed the injection of adrenalin only if glycogen was present in the organism, and thus adrenalin could be employed to deglycogenize a phlorhizinized animal. These observations have been amply confirmed (cf. Woodyatt, 219; Ringer, Dubin and Frankel, 169; Palmer, 154). It has also been shown that convulsions or anesthesia will further deplete the glycogen residues of the phlorhizinized organism.

Since animals which had been made glycogen-free by one or more

of the above procedures showed no further excretion of extra sugar upon subsequent repetition of the process after short rest periods, Lusk (124) concluded that the deglycogenized, phlorhizinized organism does not retain sugar formed from protein during a succeeding rest period, and in experiments where the extra sugar excretion is the measure of sugar formation from fed material it is not to be feared that fluctuation in the results might be due to partial retention of the substance in the form of glycogen.

Woodyatt (219) observed only a trace of glycogen in the liver, and 0.22 per cent in the muscle of a phlorhizinized dog following 12.9 grams of dextrose given intravenously. Palmer (154) reported two dogs which were made glycogen-free by phlorhizin and adrenalin administration. Each dog then received 4 grams of dextrose per kilo of body weight. Following this procedure, in one dog only a trace of glycogen was found in the muscle and the liver was negative, while in the other dog the liver contained 0.16 per cent, and the muscle 0.34 per cent, of glycogen. Csonka (42) found no increase in the glycogen content of muscle or liver of phlorhizinized dogs killed within $2\frac{1}{2}$ to 4 hours after feeding 50 grams of dextrose.

Sansum and Woodyatt (180) have proposed and employed the routine deglycogenization of phlorhizinized animals by injections of adrenalin as a preliminary step in feeding experiments designed to test the sugar-forming capacity of a substance.

While the inference that phlorhizinized animals do not have the capacity to synthesize or store glycogen has thus very generally prevailed, evidence has not been lacking that this is a mistaken conception. The view of Epstein and Baehr (57), that in the absence of the kidneys, phlorhizin in the organism actively stimulates the accumulation of glycogen in the liver, has already been noted. Paulesco and Michailesco (155) conclude that the capacity of the tissues for glycogen formation in phlorhizin diabetes is intact. After an animal had starved for a number of days a portion of the liver was removed for glycogen estimation, and no glycogen or only traces were found. Phlorhizin was then administered and on two successive days 100 to 200 grams of dextrose were given. On the following day the animal was killed, and the liver was found to contain large amounts of glycogen. Sato (185) holds that phlorhizin, despite the glycosuria, does not abolish glycogen synthesis in the liver. Torök (205) found that phlorhizinized dogs maintained in nitrogen equilibrium on diets of ox flesh and potatoes, and killed 6 days after phlorhizin, showed unusually high glycogen content of liver

and muscles. Junkersdorf (105) gave phlorhizin subcutaneously on 3 successive days to dogs which had undergone a preliminary seven-day fasting period. Those dogs which were killed 7 hours after the last phlorhizin dosage showed less glycogen in liver and muscles than those killed 24 hours after the last phlorhizin injection; new glycogen must have been formed in the interval. Less fat infiltration was observed in the second lot of dogs than in the first. In this connection Nash (148) has called attention to a circumstance which must have been evident to others who have analyzed the urine of short periods, that in many experiments on phlorhizinized dogs the dextrose-nitrogen ratios for short periods show considerable fluctuation, usually being lower at night and higher in the early day periods when the animal is more active. It is also notable that after periods of forced exercise, or other procedures calculated to deglycogenize the animal, the D:N ratios are for a time lower than the average. Cori (35) has recently suggested the possibility that sugar given to phlorhizin-poisoned animals may be temporarily stored as glycogen, even though the sugar is finally quantitatively recovered in the urine.

Ringer, Dubin and Frankel (169) discovered that glucogenetic substances like glycocoll, alanin, lactic acid, and propionic acid, when administered to adrenalized and phlorhizinized dogs yield less than one-half the amount of dextrose (as judged by the excretion in the urine) than they do ordinarily. One phlorhizinized dog which had been deglycogenized by adrenalin received subcutaneously at different periods doses of sodium lactate and sodium propionate. The animal was later killed by bleeding under ether anesthesia (a deglycogenizing procedure) and the glycogen content of the muscle was found to be 0.039 per cent. In another series of experiments phlorhizinized dogs were rendered glycogen-free by adrenalin injections and were then allowed to continue fasting under the influence of phlorhizin alone. The animals were killed 3 days after the deglycogenization and the muscles were found to contain the following amounts of glycogen: 0.020, 0.033, 0.023, and 0.039 per cent. In one animal which was kept for 5 days after the deglycogenizing process the muscle contained 0.069 per cent of glycogen. The authors cite these experiments as proof that fasting diabetic dogs, even after they have been completely deglycogenized, possess the power of glycogen formation.

A study of the extent to which glycogen storage may occur in maximally phlorhizinized dogs, following the oral administration of dextrose, was undertaken by Nash (148). Sixty grams of dextrose were given in

two equal doses at an interval of 3 hours, and the animals were killed 3 to 4 hours after the last sugar feeding. Earlier observations that an excessive hyperglycemia occurs under such conditions were confirmed. Having regard to the deglycogenizing effect of anesthesia, the animals were killed by a blow on the head, and the tissues were removed for glycogen estimation as speedily as possible. Under these conditions the muscle glycogen in per cent was found to be 0.467, 0.413, 0.870 and 0.497; while the liver glycogen, in the corresponding order of animals, amounted to 1.96, 1.23, 3.65 and 1.11 per cent. In preceding control periods the same animals had eliminated in the urine from 88 to 107 per cent of similar amounts of ingested dextrose. While any attempt to "balance the equation" between the quantities of sugar retained and glycogen stored in these experiments involves obviously uncertain factors, nevertheless an illustrative calculation may be of some significance. Dog 20, which had received 30 grams of dextrose 6.5 hours before death, and a second dose of 30 grams of dextrose 3.5 hours before death, excreted in the urine for this period 30 grams of extra sugar. The liver at autopsy weighed 442 grams and contained 3.65 per cent of glycogen, or a total equivalent of about 16 grams of dextrose. The animal at death weighed 13.3 kilos, as compared with a pre-experimental weight of 14.7 kilos. The muscle glycogen was 0.870 per cent, which is probably at least 0.5 per cent above what it would have been had no dextrose been given (cf. Ringer, Dubin and Frankel, above). It would thus appear that the glycogen excess of the muscle tissue was ample to account for the remaining 14 grams of the sugar fed.

There can be no question that the phlorhizinized dog is able to synthesize and store glycogen extensively in a condition of hyperglycemia, and to a lesser extent even after deglycogenization and a continuing fasting hypoglycemia. Hence it would seem that procedures calculated to deglycogenize animals beyond the "equilibrium" stage which is reached with phlorhizin and starvation alone are contraindicated as a preliminary to subsequent feeding tests, where the recovery of "extra" sugar is the critical factor.

3. Ketosis: Lusk (126) has called attention to the usual mild ketosis in phlorhizin diabetes, and has suggested that the intensity of ketosis depends upon the species of the reacting organism. Friedemann (67) finds only in the monkey a starvation ketosis comparable in degree to that of man. Some phlorhizinized dogs, however, appear to be susceptible of a very severe ketosis. Nash (148) reported several dogs in which, with regard for the relative weights of the animals, the extent

of the ketonuria was comparable with that occurring in the more severe cases of human diabetes. One dog, weighing 16.5 kilos, excreted in the urine of a 24 hour period 10.2 grams of total acetone bodies expressed as acetone. This animal was unusually fat; and the present author is inclined to agree with Junkersdorf (106) that the fatty state of the animal is a considerable factor in determining the degree of the ketosis in the phlorhizinized dog.

Geelmuyden (76) observed that the ketonuria of a fasting, phlorhizinized dog was diminished when meat or bread and milk were fed. Baer (12) has reported similar experiments. Lusk (124) has noted that the animals used by Geelmuyden and by Baer were for the most part not completely diabetic, and their results might be explained on the assumption that sugar was burned in the organism. Benedict and Osterberg (17), however, found that the ingestion of moderate amounts of protein by fully phlorhizinized dogs practically abolished the ketonuria, while the D:N ratios in the urine showed that the effect could not be accounted for by ascribing it to sugar combustion.

Allen and Wishart (8) have stated that when a certain stage of phlorhizin intoxication is reached carbohydrate administration may nearly or completely clear up the ketosis, but does not restore the normal plasma bicarbonate or save life. The failure of protein or carbohydrate feeding to abolish immediately an established ketonuria was attributed by these authors to the possibility that most of the available sugar was used first for glycogen formation. The animals of these experiments were apparently not maximally phlorhizinized, and it was not determined whether the sugar given was quantitatively eliminated.

Wierzuchowski (215) was the first to claim that administration of sugar (dextrose or levulose) causes the disappearance of ketone bodies from the blood and urine of completely phlorhizinized dogs for a period of 9 to 24 hours, in spite of the fact that the sugar given may not be oxidized. "Thus," according to Wierzuchowski, "the 'fire of carbohydrates' is not always necessary to oxidize completely the end products of fat metabolism in the phlorhizinized dog, but a mere increase in the quantity of glucose is sufficient to do so, possibly, by contact action between it and the ketone bodies." There was a coincident improvement in the clinical state of the animals. The degree and duration of these effects were found to be favorably influenced by the amount of sugar administered. While the quantitative recovery of the sugar in these experiments was not reported, it may be inferred from later references (Wierzuchowski, 216, 217) that this amounted to only

about 80 per cent. In fact, this author appears to have recanted his earlier opinion, and, in a later publication (217), announces the conclusion that at least a part of the sugar must have been burned.

In experiments carried on independently and published shortly after Wierzuchowski's first paper on the subject, Nash (148) also came to the conclusion that administration of dextrose to fully phlorhizinized dogs would abolish or greatly depress the ketosis, without oxidation of the sugar occurring. Thus, a dog which was excreting 330 mgm. of total acetone per hour was given by stomach tube a water solution of 30 grams of dextrose, of which 99.5 per cent was recovered during the succeeding 24 hours. In successive four-hour periods following the sugar dosage the hourly rate of excretion of total acetone bodies was 132, 34 and 104 mgm.; and in the next 10 hour period, 546 mgm. In another case the urine was negative for acetone after the oral administration of 30 grams of dextrose, although 99.2 per cent of the sugar was eliminated in the urine. In still another dog which was excreting about 100 mgm. of total acetone per hour, the oral administration of 25 grams of dextrose had completely abolished the ketonuria within 2 hours, and the urine remained negative for 6 hours. Here there was 107 per cent recovery of the sugar. The lowest recovery in 9 typical experiments was 88 per cent; and of a total of 335 grams of dextrose fed in these 9 experiments, 312 grams were eliminated in the urine, or an average of 93 per cent.

Similar effects upon the ketosis of the fully phlorhizinized human do not follow carbohydrate feeding, if such a conclusion may be based upon a single experiment. In a case of human carcinoma, in a man who was completely phlorhizinized (Benedict and Lewis, 16), the acidosis was not reduced by meat or glucose ingestion (a personal communication from S. R. Benedict quoted by Wierzuchowski, 217).

Closely paralleling the repression of the ketosis of fasting phlorhizinized dogs following ingestion of sugar, is a sharp drop in the inorganic phosphorus of the blood (Nash, 148). Coincidently the inorganic phosphorus of the urine diminishes rapidly, and most frequently disappears entirely. A definite renal threshold for phosphate is indicated. The larger the dosage of sugar the more pronounced and prolonged is the effect upon the urine phosphates. During this period of heavy sugar excretion the urine reaction changes from strongly acid to very faintly acid, or neutral. It is known that these effects are duplicated in the normal animal (Harrop and Benedict, 89; and numerous other authors). Harrop and Benedict have suggested that the phosphate withdrawn into the tissues is concerned with an intermediary

stage in the storage of carbohydrate as glycogen, which, as has been shown, occurs also in the phlorhizinized animal. The thought presents itself, that the "alkaline tide" after meals may be the reflection of such a process. The prompt recovery of the alkaline reserve in the phlorhizinized dog after dextrose feeding may not be due entirely to the burning of the ketone bodies. It is possible that the elevation in the carbon dioxide combining power of the blood in human diabetics after insulin administration likewise may be largely attributable to glycogen synthesis and the withdrawal of the blood phosphates. Henderson (92) has presented the idea that the presence of carbohydrate in the tissues is a controlling factor in the regulation of blood alkali.

Allan, Dickson and Markowitz (2) have asserted that the amount of phosphorus excreted in phlorhizin diabetes during fasting is much in excess of the yield from the protein catabolism, and must in part be withdrawn from the reserves in the bone.

It cannot have escaped the observation of any who have worked extensively with phlorhizinized animals that carbohydrate or meat feeding effects a pronounced, though temporary, improvement in the clinical condition. Dogs in an extreme stage of diabetic coma may thus usually be restored to a surprising appearance of normality. Deuel and Chambers (48) have reported that the mere ingestion of dextrose by the fasting phlorhizinized dog restores its muscular power within a few minutes even though the sugar was not burned as indicated by its complete excretion in the urine. Wierzuchowski (215) and Nash (148) find that the improved state of the animal coincides with repression of the ketosis and diminution of the acidosis, and the latter author believes that the underlying mechanism of this series of events is the storage of glycogen in the tissues. Nash (148) has called attention to the fact that, after these temporary, favorable effects, as the sugar is excreted, and the blood sugar falls again, and the glycogen is again rapidly drained from the tissues, the ketosis picks up promptly at about the level from which it was suddenly abolished, and the subsequent condition of the animal is worse than if no sugar had been given. It is as though the organism which is able to accommodate itself to a slow progressive development of ketosis and acidosis, cannot tolerate so readily a sudden reversion from one extreme to the other. Human diabetics, under insulin control, pass readily into coma when this control is briefly removed.

Friedemann, Somogyi and Webb (69, 70) have made the point that the dog is not a suitable animal in which to study the relation of car-

bohydrate to antiketogenesis. Their results are interpreted as indicating that, with the possible exception of fasting phlorhizinized dogs, the dog is able to oxidize acetoacetate without intervention of the carbohydrate metabolism. Long continued phlorhizin effect and starvation decrease the normal tolerance from 30 to 50 per cent. Allen and Wishart (8) find that injections of acetone bodies produce a greater ketosis and more severe symptoms of intoxication and injury in phlorhizinized dogs than in normal animals. The susceptibility of fasting phlorhizinized dogs to ketosis is not altered by the Eck fistula, according to Allen and Ebeling (6), which is evidence against the view of the exclusive or predominant formation of acetone bodies in the liver. Marriott (133) found that acetoacetic acid can be readily converted by the phlorhizinized dog into d, l-oxybutyric acid, but the reverse change is difficult. The dextro-component of d, l-oxybutyric acid can be utilized even by the diabetic organism, and hence only the levo-oxybutyric acid appears in diabetic urine.

4. Lactic acid formation: Embden (54) has suggested that in the phlorhizinized organism carbohydrate cannot be oxidized because it cannot yield lactic acid. Experiments by Embden and Isaac (55) indicate that the excised liver of phlorhizinized animals has lost its normal capacity to change dextrose to lactic acid. Embden, Schmitz and Meincke (56), however, found lactic acid present in dog's muscle after 4 days of phlorhizin. And Woodyatt (219) has reported an increased amount of lactic acid in excised muscle of a phlorhizinized dog whose ureters were clamped.

The question has been carefully studied recently by Loebel, Barr, Tolstoi and Himwich (118). These authors subjected completely phlorhizinized dogs to strychnin convulsions and found that the exertion which is thereby induced is accompanied by an accumulation of lactic acid in the blood to almost as great an extent as in the normal dog under similar conditions. The largest absolute increase in the blood lactic acid in the control series was from 41 mgm. to 147 mgm. per 100 cc., while in the phlorhizin series the maximal increase was 72 mgm. In phlorhizinized dogs which had been rendered glycogen-free by adrenalin, the results were more variable. Only two out of six dogs so prepared were able to perform vigorous work under the influence of strychnin, and in these the lactic acid was increased 41 and 47 mgm., respectively. In three of these dogs the blood lactic acid was not appreciably changed. Such results are obviously of importance not only to theories of muscle contraction but to the question of the mechanism

of phlorhizin action. Loebel, Barr, Tolstoi and Himwich believe that, regardless of the mechanism which may be involved in phlorhizin diabetes, the loss of the function of carbohydrate oxidation is as complete as in any known condition. The fact that lactic acid may still be formed by such an animal is evidence that the defect in phlorhizin diabetes is not in the formation of lactic acid from carbohydrate. The authors suggest that even when the original store of carbohydrate in the muscle is completely exhausted by adrenalin administration, a new supply, elaborated from protein, may be utilized to replenish the muscle glycogen, or the sugar derived from protein during the experiment may go through a lactic acid stage. Another possibility is indicated from the results of Embden and Isaac (55) who showed that in dogs, despite prolonged fasting and treatment with phlorhizin and strychnin, the muscles retain a considerable store of substance—other than glycogen—which will produce lactic acid. The failure to burn carbohydrate at a time when the animal can form lactic acid is interpreted by Loebel, Barr, Tolstoi and Himwich as indicating: a, that the defect in phlorhizin diabetes lies in the oxidation of lactic acid; or b, that lactic acid is not an intermediary in carbohydrate oxidation, but is only formed in the anoxidative breakdown of carbohydrate. The following hypothesis is therefore put forward by these authors: During the contractile phase of muscular activity energy is supplied by the exothermic chemical reactions which result in the formation and neutralization of lactic acid. These reactions occur even during complete phlorhizin diabetes and glycogen depletion. During the recovery phase the lactic acid is reconverted to glycogen by means of energy derived from the processes of oxidation. In phlorhizin diabetes fat must furnish the chief, if not the only, source of energy during the recovery phase. Quite similar results and conclusions have been reported by Doisy, Briggs, Weber and Koechig (51), and by Weber, Briggs and Doisy (212) from experiments on depancreatized and on phlorhizinized dogs.

5. The respiratory exchange: The respiratory quotient of an animal is very generally regarded as the most infallible criterion of carbohydrate oxidation. Such data as have been accumulated until quite recently from calorimeter-respiration experiments on phlorhizinized animals, have been taken as showing that by this test also carbohydrate is not burned in such an animal. Thus, Lusk (126) found in a fasting, phlorhizinized dog an initial respiratory quotient of 0.716, and in the first and second hours immediately following the ingestion of 10 grams of dextrose quotients of 0.75 and 0.67, respectively. In another case,

one hour after the ingestion of 70 grams of dextrose the respiratory quotient was 0.72 instead of above 1.0 as in a normal dog. The heat production remained unchanged. Ringer (175) found that a basal quotient of 0.711 was unchanged in four hours after giving 40 grams of dextrose to a dog on the fifth day of phlorhizin diabetes. On the other hand, Gaebler and Murlin (74) found in the large majority of experiments, in which from 20 to 27 grams of dextrose were given orally to otherwise fasting, phlorhizinized dogs, an increase in the respiratory quotient above the basal level. An average of five experiments shows the basal quotient at 0.668, and 2 to 3 hours after sugar feeding, 0.735; the greatest change was from a quotient of 0.661 to 0.755. The average increase of 0.067 in the respiratory quotient in these control experiments is not impressively less than the average increase in subsequent experiments when insulin and sugar were given together (see below), yet Gaebler and Murlin interpret the latter values as positive proof of carbohydrate oxidation.

The present author is not convinced of the implicit reliability of the respiratory quotient as an index of the qualitative and quantitative metabolism of an animal for short periods in which gross and sudden changes in the metabolism are obviously occurring. The conditions are exceedingly complex. Lusk (129) has shown that the exact determination of the theoretic respiratory quotient in diabetes associated with ketosis is at present impossible, and has warned " . . . . against the too literal interpretation of respiratory quotients obtained under grossly abnormal circumstances." Palmer (154) has emphasized that under the usual conditions there is a possible error of such magnitude in the determination of the respiratory quotient that a man might burn 50 grams of dextrose at the rate of 2 grams per hour in 24 hours without detection in the calorimeter; on the other hand an organism might be accredited with the combustion of more sugar than actually occurs. Nash (148) has called attention to some of the special complications which apparently should be taken into account. If the ketone bodies, which disappear so promptly in the phlorhizinized dog after administration of sugar, are oxidized, this should be a factor operating to elevate the respiratory quotient to some extent. However, the resultant liberation of alkali presumably combined with these bodies would be expected to unite with and retain carbon dioxide, a process which would affect the quotient in the opposite direction. Furthermore, the value of the diabetic respiratory quotient for protein is about 0.64 (Lusk, 126), so that a relative decrease in the protein fraction of

the total metabolism should operate in the direction of elevating the total respiratory quotient. It is well established that carbohydrate spares the protein metabolism of the phlorhizinized animal to a greater extent than can readily be accounted for on a dynamogenetic basis (Ringer, 161). Therefore, because of the nitrogen lag (compare, for example, Nash and Benedict, 149), the nitrogen output of relatively short calorimeter periods following immediately upon administration of sugar or meat cannot possibly reflect accurately the protein metabolism of such periods. It follows that non-protein respiratory quotients, particularly those of the intermediary hours, are not valid in such experiments. Still another possibility that would seem worthy of consideration is the formation of fat from carbohydrate. While the opinion seems to prevail that fat synthesis from carbohydrate occurs only with respiratory quotients above 1.0, there is no obvious or demonstrated reason why this should be so. Is it not likely, for example, that animals which fatten on a meat diet may do so at a normal respiratory quotient? It has been shown that sugar feeding may lead to quite normal accumulations of glycogen in the tissues of phlorhizinized animals: is the pathway to fat synthesis completely blocked until some definite concentration of carbohydrate is present in the tissues?

Wierzuchowski (217) has recently reinvestigated the effect of dextrose upon the respiratory quotient of phlorhizinized dogs. In three experiments upon two dogs 20 grams of dextrose were given just before the animal was placed in the calorimeter, and in two experiments 40 grams of dextrose were given in two equal doses, 4 hours apart, the animal being put into the calorimeter shortly after the second feeding. In the latter experiments the first dose of sugar was presumed to have abolished the ketosis and raised the alkaline reserve of the blood to normal, thus obviating one of the complications already discussed. The basal quotient in all cases was very close to 0.700. After a single dose of 20 grams of sugar the quotient during the first and second hours was about 0.750, but fell in the third hour to the basal level. In the experiments where 40 grams of sugar were administered the quotients during the first four hours after the second dose were, in one case, 0.801, 0.741, 0.768, 0.710; and in a second case, 0.771, 0.802, 0.702, 0.702. Wierzuchowski calculates that in these experiments the total sugar oxidized was 2.30 grams, 4.08 grams, and 2.80 grams, respectively. The corresponding ratios of *ketogenic mols : glucose mols* (Schaffer, 191) were estimated, from a computation of the mixture of materials burned after sugar ingestion, to be 1.15, 0.80, and 0.55. It may be

noted that in the one instance where the elimination of the administered sugar is reported, only 26.79 grams of the 40 grams given were recovered, although the calorimeter could account for the combustion of but 2.80 grams.

In a personal communication Professor Graham Lusk states that Wierzuchowski's experimental work has recently been confirmed by H. J. Deuel, Jr. and H. E. C. Wilson, working in Lusk's laboratory. A dog was fed with a standard diet plus 50 grams of cane sugar, and 18 hours afterwards respiratory quotients of about 0.95 were found. The following day, the same diet having been given 18 hours before, 1 gram of phlorhizin was administered subcutaneously in oil, and 1 gram subcutaneously in 10 cc. of 1.2 per cent sodium carbonate solution. The animal was put in the respiration apparatus at once. The respiratory quotients began at 0.95 and ran at that height in the early hours of the experiment; the quotient was about 0.80 during the ninth hour after phlorhizin. The D:N ratio in the urine was high, approximately 10:1. Two days later the respiratory quotients had fallen to 0.69, at which time the administration of 16 grams of dextrose caused an oxidation of about 10 per cent of it. The experiment was repeated three times with practically the same result. When sugar was fed to otherwise fasting and phlorhizinized dogs there was practically always some rise in the respiratory quotient which subsided usually in four hours. These increases were apparent with as small an amount of dextrose as 10 grams but not with 5 grams of the sugar. The respiratory quotients were followed also in nephrectomized animals which received phlorhizin immediately after the operation or beginning one day later. No food was given after removal of the kidneys. In one animal the respiratory quotient was obtained daily from the third to the sixth day after nephrectomy, or the second to fifth day after phlorhizin was first injected, and the quotient was never found to be below 0.720. Usually the quotient was 0.730 or higher, or at a level very appropriate for a normal animal which had been fasted for a corresponding period. Upon giving a small amount of dextrose to one of these animals there was a rise in respiratory quotient to 0.86. The rate of protein metabolism in these nephrectomized animals was not affected by the administration of phlorhizin as judged by the rate of increase in the non-protein nitrogen of the blood. Furthermore, the nephrectomized dogs did not have an acetone breath even the fifth day of phlorhizin administration.

Whether or not it may be concluded finally on the basis of the re-

spiratory exchange that there is no absolute blockade of the carbohydrate burning capacity of the phlorhizinized organism, the evidence is already sufficient that this capacity is at least extensively impaired.

d. The effects of insulin in phlorhizin diabetes: Woodyatt (221) has suggested that there are two distinct types of sugar reaction in the body, destructive and transformative; it is only the first of these that disappears in diabetes. The reason, according to Woodyatt, is the lack of something derived from the pancreas which normally does for sugar what is accomplished *in vitro* by sufficiently concentrated alkali. In diabetes mellitus there is a hyperglycemia only of molecular or undissociated, inert sugar, whereas in phlorhizin diabetes there is an absolute hypoglycemia as regards sugar of all forms. Here also destructive reactions disappear. But in this case the feeding of dextrose in high concentration causes the reappearance of oxidative reactions, so that here the analogue of alkali derived from the pancreas cannot be regarded as lacking.

This prophetic vision of insulin has now been put to the test. Although Allen (4) predicted " . . . . with perfect positiveness that insulin will have no influence upon phlorhizin glycosuria," it is now recognized that insulin does show a profound, though temporary, influence upon the phlorhizinized organism.

Nash (147) was the first to report observations of effects produced by insulin in the maximally phlorhizinized and fasting dog. In a 15 kgm. dog which had been fasted for four days and phlorhizinized for two days, the D:N ratio for the last control 24-hour period was 3.58. The injection of 10 clinical units of insulin reduced the blood sugar within three hours to 48 mgm. per 100 cc. from the control level of 75 mgm.; four hours later the blood sugar value was 47 mgm.; and after a further 16 hours the value was 62 mgm. With the falling blood sugar the excretion of sugar fell off rapidly, until in the second two-hour period after insulin administration the hourly rate was just one-half of the control rate. This low rate of elimination persisted for another two hours, then recovered sharply, and for a time exceeded the control rate. The rate of nitrogen excretion also fell, but more slowly, and recovered more slowly. This was to be expected if the protein metabolism was spared, and the decreased nitrogen elimination was not due to a specific retention, since it has been shown (Nash and Benedict, 149) that the phlorhizinized dog eliminates sugar more rapidly than urea, even when both substances originate simultaneously in the organism. Consequently there was a great disturbance in the D:N ratios,

which first fell and then rose above the normal value, and finally, after about 20 hours, were again stabilized at the normal level. The extreme variations in the D:N quotient during this period were 2.47 and 6.77. Total sugar output for the 24-hour insulin period was 34.84 grams, as compared with 38.01 grams in the preceding 24 hours, and 33.68 grams in the following 24-hour period. There was thus little indication of sugar consumption under the influence of insulin. The diminished nitrogen excretion was attributed to a sparing action upon the "dextrose nitrogen" quota (Ringer, 161) of the protein metabolism, occasioned by the temporary concentration of carbohydrate in the tissues as glycogen or in some other form. The possibility was also suggested that Ringer's "complementary nitrogen" fraction of the protein metabolism might have been spared by an increased or more complete combustion of fat, since it was observed that the urines became strikingly less acid or neutral following the insulin injections.

In similar studies carried out at the same time and reported almost simultaneously with the above, M. Ringer (175) came to quite different conclusions. Ringer gave dextrose with insulin to the animals of his experiments, and in one instance followed the respiratory exchange and heat production in the Lusk calorimeter. In the calorimeter experiment, when the dog received 40 grams of sugar and 20 units of insulin one hour previously, the respiratory quotient rose from a basal value of 0.711 to a maximum of 0.751, with an average for four hours of 0.736. On the following day, 20 grams of sugar and 20 units of insulin were given 3 hours before the calorimeter observations, and 40 grams of sugar and 12 units of insulin one hour beforehand. In this case the maximal quotient was 0.837, and the average quotient for 4 hours of observation was 0.823. Here, Ringer calculates, there was an oxidation of over 2 grams of sugar per hour. In other experiments, Ringer assumes that anything less than a 90 per cent recovery of administered dextrose represents sugar burned under the influence of insulin, and on this basis finds in 6 dogs an average of 0.64 gram of dextrose oxidized per unit of insulin; the extremes were 0.38 gram and 0.72 gram. Ringer proposed, therefore, the use of phlorhizinized dogs for assaying insulin directly in terms of carbohydrate utilized. It may be noted in this connection that Simmich (194) finds phlorhizinized dogs do not afford a suitable means of standardizing insulin as the results are too irregular.

In the above experiments, Ringer noted that insulin not only prevents the development of the hyperglycemia which would otherwise follow in phlorhizinized dogs ingestion of such amounts of sugar, but actually

intensifies the existing hypoglycemia. Abolition of the ketonuria was observed. The probable storage of glycogen was suggested. And a greater and more prolonged fall in the protein metabolism was shown when insulin was given with sugar than when sugar was given alone.

These results led Ringer to propose that the mechanism of phlorhizin action is an effect upon the pancreas, preventing the production of insulin. This theory was promptly endorsed by Ets (60). However, such an hypothesis was not reconcilable with a number of well-established facts, among which may be mentioned the increased glycosuria and lowered blood sugar following phlorhizin injection in depancreatized dogs (Minkowski, 140; and others); the failure to detect histological changes in the pancreas of phlorhizinized animals (Allen, 3; 4); and the historical finding of Zuntz (223) that a temporary, unilateral glycosuria might be produced by injecting phlorhizin into the renal artery of that side. Nash and Benedict (150) soon showed that insulin might be obtained from the pancreas of dogs even after prolonged and maximal phlorhizin effect. This finding was shortly confirmed by Cori (37) for phlorhizinized cats. Stammers (198), however, believes that Ringer's view is not necessarily irreconcilable with the finding of insulin in the pancreas of phlorhizinized animals.

Cori (33) studied the influence of insulin in phlorhizinized rabbits. He found a fall in the blood sugar and in the excretion of sugar. When the blood sugar was maintained at a low level by repeated insulin injections the sugar excretion fell at times to one-sixth of the control rate. Cori believed that the observed effects might be due to a conversion of sugar into glycogen or fat, but sufficient after-periods were not allowed to determine whether retained sugar was later excreted. In subsequent experiments, however, Cori (34, 35) was able to show by direct analysis of the liver in starving phlorhizinized rabbits and cats a considerable storage of glycogen under the influence of injected insulin. Synthesis of glycogen reached its maximum in about 6 hours after insulin, and coincided with low D:N ratios in the urine. Later the accumulated glycogen disappeared gradually from the liver and gave rise to extra sugar in the urine. Cori thinks it possible that sugar given to phlorhizinized animals may be stored temporarily as glycogen, even though the sugar is finally quantitatively recovered in the urine, and points out that this behavior is of importance in evaluating results obtained with the measurement of the respiratory exchange in starving animals.

It was also shown by Cori (36) that insulin has no effect on the lactic acid of the blood of phlorhizinized rabbits.

Page (153) has reported that sucrose and insulin given to phlorhizinized dogs raises the respiratory quotient within two hours, and depresses the excretion of nitrogen. The technique and data of these experiments, however, indicate that the animals were by no means completely diabetic.

Colwell (32) described two experiments in which, by uniform milk and cream feedings, phlorhizinized dogs were maintained at a constant glycosuric level for 6 days. Insulin injections produced depressions in the sugar output corresponding to 0.14, 0.20 and 0.08 gram per unit of insulin given. The much larger retentions found by Ringer (175) are criticized for lack of proper control and sufficient after-periods. His own findings Colwell is disposed to explain as due to impairment of elimination due to toxic effects on the kidneys or tissues at large, following the administration of insulin preparations.

Gaebler and Murlin (74) studied the influence of insulin, administered orally and subcutaneously, upon phlorhizin diabetes in dogs. The authors claim for the oral administration of insulin and dextrose a positive though moderate effect in reducing the sugar output, sparing of protein and increase in the respiratory quotient. The data, particularly with reference to the respiratory quotient, are not very convincing. No quotient appears which is decisively more increased above the basal than the average increase found after giving sugar alone. When dextrose was given orally and insulin injected subcutaneously the excretion of nitrogen was reduced more than when the sugar alone was given. Sugar retained amounted to from 0.28 to 0.48 gram per clinical unit of insulin. The effect upon the respiratory quotient was again scarcely convincing in the majority of experiments, in comparison with the average effect of sugar given alone. However, in two experiments on one dog (dog 8), where 20 grams of dextrose and 15 clinical units of insulin were given, the respiratory quotient reached maximal values of 0.853 and 0.834, respectively. Even the maximal effects upon the respiratory exchange were less prolonged than the effects upon the sugar excretion, and while extra sugar appeared in the urine in later periods it was not possible to account for the total sugar loss on the basis of its oxidation. These results should be compared with those obtained by Hawley and Murlin (91) in the study of the altered metabolism of normal animals under insulin treatment, where the metabolism of fat was first increased and the respiratory quotient correspondingly depressed.

An interesting theory of phlorhizin mechanism is advanced by Gaebler and Murlin. They noted that when insulin and phlorhizin were in-

jected into the same site there was much less effect of the insulin than otherwise. They believe that the explanation here is a local inactivation of the insulin by the phlorhizin. Therefore it is suggested that phlorhizin diabetes is caused in part by inactivation of insulin after it has reached the circulation or the tissues, and the prediction is made that the mechanism of the inactivation will be found to be hydrolysis of phlorhizin in the tissues thus setting free the reducing group of the glucoside sugar which in turn will neutralize the insulin activity as does glucose itself (Murlin, 144). In this connection it may be noted that Slowtzoff (195) has discovered phlorhizinase among the enzymes of the brain. To the present author it seems much more likely that the lessened effect of insulin noted by Gaebler and Murlin when injected as above may be due to slower absorption on account of the oil in which the phlorhizin is administered; indeed it is precisely to enable slower absorption that phlorhizin is injected in oil.

A comparison of the effects in fasting, phlorhizinized dogs of dextrose given alone and with insulin has been made also by Nash (148). The average elimination of sugar given with insulin was 72.5 per cent as compared with a recovery of 91 per cent without insulin. The difference, 18.5 per cent, represents an average retention due to insulin of 0.28 gram per unit. The largest retentions were where the smaller amounts of insulin were given (much this same relation appears in the work of Gaebler and Murlin (74)). In the majority of cases extra sugar elimination continued for 36 to 48 hours after giving the sugar and insulin. As judged from the nitrogen excretion there was no significant difference in the degree of effect upon the protein metabolism when 60 grams of dextrose were given alone or with 40 to 45 units of insulin. Insulin with dextrose caused usually a more prolonged effect of reduced phosphate excretion than when the sugar alone was given. Since the severity of ketosis in phlorhizin diabetes is progressively greater as the experiment continues it was impossible here to compare accurately the effects of sugar with and without insulin. There was little indication, however, that insulin intensifies the action of dextrose in reducing the ketosis; on the contrary, it was sometimes observed that the larger doses of sugar and insulin failed to abolish the ketosis completely, whereas on the preceding day this had been accomplished by a smaller dose of dextrose alone. Direct analysis of muscle and liver showed extensive deposition of glycogen following the administration of dextrose and insulin. The average value, particularly for the liver, was considerably higher than when dextrose alone was given in

the same amounts, although the largest concentration of glycogen found in the liver (3.65 per cent) was from an animal of the latter group. The most significant difference between the two groups of experiments with respect to glycogen storage was the associated hyperglycemia after sugar alone, and the coincident hypoglycemia when insulin also was given. The dog of the insulin-sugar group showing the highest glycogen values (muscle, 0.705 per cent; liver, 3.39 per cent) was killed while in a comatose state after extreme hypoglycemic reactions. The fact that hypoglycemic reactions induced by insulin may occur with such ample carbohydrate reserves in the tissues must have an important bearing upon the question of the mechanism of insulin action. Certainly in the phlorhizinized dog the amounts of sugar stored as glycogen in the muscle and liver tissues far exceed any possible amounts oxidized. Thus in a dog which had excreted during 6.5 hours but 14 grams of 60 grams of dextrose given with 40 units of insulin the combined glycogen of liver and muscle was found to be at least 35 grams. With such extensive glycogen deposition under the influence of insulin Nash suggests the possibility of fat synthesis as one factor, other than an increased oxidation of carbohydrate, which would operate to raise the respiratory quotient in such experiments. In this connection an experiment by Lublin (119) may be cited: levulose given by mouth to a healthy man did not cause as great a rise in the respiratory quotient as when insulin was given before the sugar; in the latter case the quotient rose above 1.0, wherefore Lublin concludes that insulin stimulates the formation of fat from carbohydrate.

The hypoglycemic syndrome in insulinized, phlorhizinized animals is usually introduced by a short period of excitability and hyperpnea. In some cases the animal may recover without more pronounced symptoms than these. It is quite possible that in some respiration experiments these milder reactions may have passed unobserved.

The occasional toxic symptoms and convulsive reactions of phlorhizinized animals which have been attributed to impurities in the phlorhizin preparations are now recognizable in some cases as hypoglycemic reactions. The purity of the phlorhizin preparation is nevertheless a matter of importance. Some laboratories still find too frequent D:N quotients of the order of 2.8. It is possible that old phlorhizin preparations split into phloretin and dextrose. Employing phlorhizin purified as directed by Deuel and Chambers (49) the 3.65 quotient is practically always obtainable in the dog.

Lundsgaard and Holbøll (122), who have asserted that phlorhizin

does not alter the normal state of the blood sugar, propose (121) an attractive theory of the mechanism of phlorhizin action. They find that phlorhizin in a concentration of 1 to 50,000 or greater prevents the usual effect of insulin in changing a, b-glucose to neo-glucose, when 15 grams of muscle and 20 units of insulin are employed. The phlorhizin is found to act upon the muscle complement of insulin and not upon insulin direct. These findings are confirmatory of the results obtained by Ahlgren (1). Employing the methylene-blue technique of Thunberg (204) Ahlgren reports that minute concentrations of phlorhizin abolished the oxidative increase which otherwise followed the addition of insulin and dextrose to minced muscle tissue. This neutralization of the insulin effect by phlorhizin depends upon an inactivation of the *glykomutin* (muscle complement) whose usual function it is to convert, in the presence of insulin, a, b-glucose into a more reactive form, *x-glucose* (neo-glucose). That phlorhizin does not repress the oxidative catabolism of *x-glucose* was shown by experiments in which phlorhizin was introduced some time after the addition of insulin and dextrose to the tissue mass, that is, after the conversion of a, b-glucose to *x-glucose*. Here the influence of phlorhizin upon the oxidative process was nil. It was found that the effective concentration of phlorhizin was widely independent of the insulin concentration. Ahlgren suggests that the mechanism of phlorhizin diabetes is essentially an effect upon the tissues generally. These concepts are strikingly analogous to the "Receptor" hypothesis of Nash and Benedict (149). So far, however, extensive and numerous repetitions of the work of Lundsgaard and Holbøll have failed to confirm the presence in the blood and tissues of such a substance as neo- or x-glucose.

Austin and Boyd (11) have found that insulin does not alter the ratios of polariscopic to copper reduction values in the urine of phlorhizinized, fasting dogs.

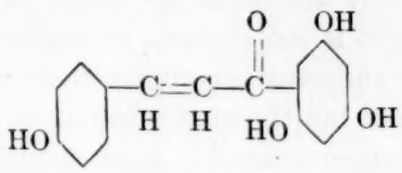
Karsner, Koeckert and Wahl (111) were unable to find an alteration in the diastatic capacity of the blood after subcutaneous injection of phlorhizin.

Anderson (9) has reported that phlorhizin, in some unexplained manner, decreases the mortality from insulin hypoglycemia in mice, but has no effect on the convulsions and other physical symptoms which accompany this hypoglycemia.

e. Miscellaneous observations bearing upon the phlorhizin process: Under the combined effects of insulin and phlorhizin there is a decrease in formation of glycuronate after administration of menthol (Friedemann and Koechig, 68).

Teschendorf (203) found an inhibition of phlorhizin diuresis in rabbits after paralysis of the sympathetic nervous system by ergotamin. The effect on the glycosuria was still more marked. He concludes that the action of phlorhizin upon the kidneys is only a part of its effect.

Franck (65), employing catalytic reduction with colloidal platinum, claims to have converted naringenin



into a dihydroderivative identical with phloretin. Contrary to expectations this phloretin gave no glycosuria in the dog. Franck finds that commercial phloretin contains up to 30 per cent of phlorhizin; after removing the latter by a tedious purification process, a phloretin preparation remained which, dissolved in soda and injected subcutaneously, produced an extraordinarily slight excretion of sugar in the urine.

Schaefer and Schmidt (186) have noted that water solutions of phlorhizin of various concentrations did not show depressions of the freezing point, and saturated solutions were dissociated only to 0.4 per cent. They decide that phlorhizin is colloidal in nature.

The preparation and chemical properties of a number of derivatives of phlorhizin have been described by Epstein and Hirschberg-Maechling (58), who sought a compound which would not show the glycosuric action of phlorhizin but would retain the assumed phlorhizin effect upon glycogen formation and blood-sugar reduction. The pharmacological study of these compounds is still to be reported.

Koppányi, Ivy, Tatum and Jung (113) have recently reinvestigated the question of avian diabetes and glycosuria. They confirm that phlorhizin produces glycosuria in the fowl.

Some interesting observations have been made by Harvey (90) upon seasonal variations in the amount of phlorhizin in plant tissues. Apple and pear trees were found to contain the greatest quantity of phlorhizin in the early summer, coincident with the period of highest metabolic activity. At such times, it is claimed, phlorhizin may increase to 20 per cent of the total solids, or 5 to 6 per cent of the fresh weight of the tissue. Pear shoots nearly always contain about twice as much phlorhizin as the corresponding tissue of the apple tree. On any given date, phlorhizin is most abundant at the tip of the shoot, and uniformly less

towards the base. The general speculative conclusion is reached that the phenol acids, upon which the synthesis of phlorhizin may depend, are a sort of by-product of metabolic activity, and phlorhizin synthesis prevents their accumulation and provides a reserve which may be drawn upon for subsequent use by the tissue.

II. PHLORHIZIN AND THE STUDY OF INTERMEDIARY METABOLISM. The usefulness of the diabetic animal in the study of the processes of the intermediary metabolism is too obvious to require comment here. Of the means available for inducing experimental diabetes phlorhizin is not only the most convenient but the most effective in respect to the degree of carbohydrate intolerance created. Even though phlorhizin diabetes may not represent a complete incapacity to burn carbohydrate it is not apparent that for this reason the *essential* validity of many important conclusions concerning the metabolic processes, based upon observations of phlorhizinized animals, can be impeached. For example, the classification of an amino acid as glucogenetic or non-glucogenetic may be determined with great certainty despite a possible partial utilization of sugar arising in the intermediary metabolism. It may be pointed out, however, that, if the phlorhizinized organism is capable of utilizing carbohydrate even to a small extent, maximal yields of extra sugar in the urine are probably more reliable than the average of several experiments. Thus, it is inferred that alanin is glucogenetic to the extent of the entire carbon content of the molecule, since as much as 95 per cent of the maximal theoretical yield has been obtained in the urine after feeding alanin to the phlorhizinized animal, although, not infrequently, smaller yields of extra sugar are obtained from alanin in such experiments.

a. The intermediary metabolism of carbohydrate: Once it was recognized that the sugar which continues to be excreted by the starving, diabetic animal has its origin in protein, the way was opened for speculation as to the mechanism of the conversion. Hypothetical intermediates, and assumed reactions in the process, could be tested readily by feeding experiments in diabetic animals which would excrete the sugar if formed. It is largely in this manner that a possible and plausible scheme of intermediary carbohydrate metabolism has been arrived at. The historical development of this scheme will not be traced here. A considerable part of the work was accomplished prior to the period represented in the present review. It is proposed now to refer briefly only to the more recent studies, some of which have been undertaken to verify earlier observations and conclusions.

The fact that the accredited intermediates in the carbohydrate process are not burned in phlorhizin diabetes indicates that the oxidative pathway is blocked by phlorhizin at some late stage.

Woodyatt (222) and Sansum and Woodyatt (183) found that glyceric aldehyde is capable of complete conversion into dextrose in the fully diabetic organism. However, they do not believe (Sansum and Woodyatt, 184) that glyceric aldehyde is a chief intermediate in dextrose catabolism. They calculate that if more than 5 per cent of the dextrose which is utilized in the normal organism, in experiments where the sugar tolerance is exceeded by intravenous injection of dextrose, was split into glyceric aldehyde easily demonstrable quantities of the latter substance should be found in the urine.

Chambers and Deuel (29) obtained a practically complete conversion of glycerol to dextrose in phlorhizinized dogs, and observed a decrease in the respiratory quotient corresponding to oxidation of the 2 atoms of hydrogen liberated in the reaction. In the rate of excretion of the sugar formed and the sparing of the protein metabolism, the reaction of glycerol was similar to that of the monosaccharides. Voegtlin, Thompson and Dunn (210) report that glycerol produces in fasting rabbits a hyperglycemia of considerable extent and duration. Goldblatt (78), however, could observe no effect of glycerol on the starvation ketosis of human subjects.

Dakin and Dudley (45) showed that methyl-glyoxal is converted into sugar by the phlorhizinized dog, and is therefore a possible intermediate between glyceric aldehyde and lactic acid. Dudley (52) has refuted Foster's assertion (63) that rabbit muscle does not contain glyoxalase and hence in rabbit muscle lactic acid presumably does not arise from methyl-glyoxal.

Dakin and Janney (47) found that when the sodium salt of pyruvic acid was given orally to phlorhizinized dogs or human diabetics, almost as much extra sugar was eliminated in the urine as after giving lactic acid itself. Subcutaneous injection resulted in a definite but relatively small increase in sugar output. The authors believe, therefore, that dextrose cannot be formed directly from pyruvic acid; but if conditions are favorable for the reduction of the latter substance to lactic acid, then dextrose may be produced. They suggest the following course of the conversion: pyruvic acid—lactic acid—methyl-glyoxal—dextrose.

Ringer (164), also, found that pyruvic acid yields dextrose in the phlorhizinized organism, but the extent of the conversion was variable, and in some cases much less than is yielded from similar amounts of

alanin or lactic acid. It was concluded, therefore, that pyruvic acid is not an obligatory intermediate in the conversion of alanin into lactic acid, and consequently alanin cannot be considered to undergo oxidative deaminization. Mayer's (134) failure to demonstrate sugar synthesis from pyruvic acid in phlorhizinized dogs and rabbits was attributed by Ringer to contamination of the pyruvic acid preparation by tartaric acid, which, as Underhill (206) has shown, practically abolishes kidney function in the phlorhizinized animal. Ringer (167) believes that pyruvic acid possesses glucogenetic properties to the extent that it may be converted into lactic acid (by reduction) or acetaldehyde (by decarboxylation), and there must be still a third possibility for its breakdown which does not result in the formation of sugar.

It was found by Ringer and Frankel (170) that administration of acetaldehyde or propylaldehyde to phlorhizinized dogs caused the elimination in the urine of larger amounts of extra sugar than could be accounted for by maximal conversion of the carbon present in the aldehydes. There was concomitantly a considerable depression of the ketonuria. The authors infer that the two phenomena are causally related, and suggest that the aldehydes may combine with the secondary alcohol radical of b-hydroxybutyric acid, thereby converting it into a glucogenetic substance. Sansum and Woodyatt (180, 181) found little or no extra sugar output following the administration of acetaldehyde to phlorhizinized dogs which had been deglycogenized by adrenalization. They explained Ringer and Frankel's results as due to hypnotic effect of aldehydes leading to discharge of glycogen. Ringer, Dubin and Frankel (169) have pointed out that these negative findings are probably attributable to storage as glycogen of the sugar formed from the aldehyde. Veltmann (209) more recently has claimed that no gluconeogenesis follows administration of acetaldehyde or ethylene glycol to phlorhizinized animals.

Dioxyacetone is both glucogenetic and antiketogenic (Ringer and Frankel, 172). In some phlorhizinized dogs the conversion is quantitative.

Woodyatt (220), Sansum and Woodyatt (179), and Cremer (40) have tested the glucogenetic character of glycol aldehyde in phlorhizinized dogs, with inconclusive results. Greenwald (83), however, in 20 out of 21 experiments, observed a rise in the D:N ratio of the urine after giving glycol aldehyde. In the one experiment made with aminoaldehyde extra sugar was obtained. On the other hand, glyoxal was without effect upon the sugar output or the D:N quotient, except that

later periods developed a sequence of toxic symptoms similar to those observed after giving glycol aldehyde, and attributable to renal damage.

Propylene glycol, according to Hering (93), is glucogenetic in the phlorhizinized organism.

That an alcohol, aldehyde, or ketone radical in the molecule of a substance is not prerequisite to its conversion into dextrose was first shown by Ringer (162), who injected phlorhizinized dogs subcutaneously with water solutions of sodium propionate and recovered in the urine in each case slightly more than the theoretical maximum amount of extra sugar. The results justified the conclusion that all of the carbon of propionic acid is convertible to sugar. Greenwald (80) obtained quantitative conversion of propionic acid to dextrose in a human diabetic with a D:N quotient of about 3.5.

Greenwald (81) has determined that citric acid is quantitatively converted to dextrose by phlorhizinized dogs and human diabetics.

Schwenken (189) finds that acrylic acid causes in phlorhizinized dogs an increase in sugar output to a degree indicative of the conversion of all three carbon atoms of the acid.

Inosite is apparently converted, slowly and incompletely, into dextrose (Greenwald and Weiss, 84).

Csonka (43) has found that starch is not utilized by completely phlorhizinized dogs, but is eliminated quantitatively in the urine as extra sugar. Inulin, however, is without effect upon the sugar excretion (Lewis and Frankel, 117).

Sansum and Woodyatt (182) undertook to assay the food value of commerical glucose on the basis of extra sugar excretion by phlorhizinized dogs to which the material was fed. The authors were not able to establish satisfactory control recovery of pure dextrose, probably because of renal injury and excessive glycogen depletion caused by preliminary adrenalization. Olmsted (152) in a similar manner has investigated the available carbohydrate of several vegetables used commonly in low carbohydrate diets. The values obtained from feeding experiments in phlorhizinized dogs agreed surprisingly with *in vitro* diastase hydrolysis analyses.

Deuel, Mandel and Waddell (50) have employed the phlorhizinized animal to prove that "glucosane" is without merit as a food for diabetics.

Deuel and Chambers (49) show that the hourly elimination of extra dextrose by phlorhizinized dogs is practically the same after the ingestion of 16 grams of dextrose, levulose or galactose; whereas extra sugar after lactose appears much more slowly.

One of the most interesting and theoretically promising relations of the study of the intermediary carbohydrate metabolism was revealed by Ringer (165) in the discovery that dextrose is formed from valerianic and heptylic acids. It was indicated that these acids give rise to dextrose because, by b-oxidation, propionic acid would be formed as an intermediate. Associated with the gluconeogenesis was a coincident antiketogenic process. Under the same experimental conditions, butyric acid and caproic acid produced an increase in the elimination of acetoacetic acid and b-hydroxybutyric acid, and were without effect on the sugar elimination. It thus appeared that fatty acids with an even number of carbon atoms would always be ketogenic, while those with an odd number of carbon atoms would yield dextrose from the final 3-carbon chain reached through b-oxidation. The authors anticipated that higher fatty acids with 15 or 17 carbon atoms should be of the utmost value in the treatment of diabetes mellitus. Some years later the synthetic preparation of such odd-carbon fats was developed by others on a commercial scale, and the product was marketed under the name "Intarvin." It is to be regretted that commercialization of this work, and the contemporary discovery of insulin, have prevented a sufficiently extensive test of Ringer's theory. Such results as have been obtained with intarvin in experimental and human diabetes are conflicting (cf., for example, Benedict and West, 15; Benedict, Ladd, Strauss and West, 14; Kahn, 108; Lundin, 120; Modern, 141).

b. The protein metabolism: The intermediary metabolism of the amino-acids, and the pertinent literature, have been adequately summarized by Lusk (129). The present evidence is that all of the carbon of glycocoll, alanin, serin, and cystin is converted into dextrose, while aspartic acid, glutamic acid, arginin, and prolin yield dextrose to the extent of 3 carbon atoms. Leucin, phenylalanin and tyrosin are ketogenic. The fate of valin, lysin, histidin and tryptophan is obscure. It may be noted that Greenwald (82) claims norleucin may give rise to sugar in the phlorhizinized dog.

Among those who have contributed to the study of the mechanism of amino-acid metabolism may be mentioned Lusk (124), Dakin (44), Dakin and Dudley (46), Ringer (124), Ringer, Frankel and Jonas (173, 174), Csonka (41), Nitsche (151), Steinhausen (199). Corley (38) has recently tested several synthetic amino-acids in phlorhizinized dogs, and obtained results which he interprets as indicating that a-amino-acids are frequently broken down through the stage of a fatty acid having one less carbon atom.

It has been pointed out by Lusk (129) that, on the basis of analyses of muscle tissue, not enough sugar can be calculated from the amino-acids known to be glucogenetic to account for the D:N quotient 3.65 which is characteristic of protein breakdown in the phlorhizinized dog and the completely diabetic human. The theoretical quotient so calculated is much nearer the 2.8 value found in the depancreatized dog and the phlorhizinized cat, rabbit, goat. The 3.65 quotient represents an additional amount of sugar whose origin is largely unexplained. No adequate explanation has ever been offered for this most interesting variation of the D:N quotient among different species; and the question remains one of the most fundamental unsolved details of the mechanism of phlorhizin action.

Janney and Csonka (104) made the interesting observation that, whereas phlorhizinized rabbits show an average D:N ratio of 2.8, when the muscle protein of the rabbit is fed to the phlorhizinized dog 60 per cent of it is convertible into dextrose. These authors have averaged the D:N ratios of 227 periods (12 or 24 hours periods) as reported by various workers for fully phlorhizinized dogs, and arrive at the value 3.43. They suggest that variations in the D:N ratio in dogs may be due in part to varying amounts of nitrogenous extractives in muscle. The existence of the 2.8 ratio in phlorhizinized animals is attributed not to failure to form the maximal amount of glucose from protein, but to the synthetic utilization of a portion of it; whereas in phlorhizin diabetes exhibiting the higher quotient, both the power of complete oxidation of dextrose and its synthetic utilization may be lost.

Janney and Blatherwick (102) and Janney (100) have determined the amounts of sugar produced from various proteins, both vegetable and animal, when fed to the phlorhizinized dog. The muscle of man, dog and ox yielded 58 per cent of dextrose. The highest conversion, 80 per cent, was of gliadin, and the smallest, 48 per cent, of casein.

1. Time relations in the protein metabolism: The observation by Janney (100), confirming the earlier observation by Reilly, Nolan and Lusk (158), that after protein feeding to the phlorhizinized dog the sugar excretion attains its highest rate before the nitrogen elimination reaches a maximum, has been interpreted as indicating a more rapid synthesis of sugar than urea in the metabolism of the amino-acids. As Janney pointed out, the time relations of nitrogen excretion in such experiments are not essentially different from those for normal animals. Ringer (161) has claimed that the nitrogen is the most variable factor in the D:N quotient. Csonka (41) has noted, also, that the rapidity

of absorption and elimination of ingested dextrose by the phlorhizinized dog was almost the same as the rate of absorpton of iso-glucogenic quantities of glycocoll or alanin and elimination of the synthetic sugar produced from them after their deaminization. Elimination of extra nitrogen formed in the process was less rapid, and Csonka has emphasized the fallacy of basing calculations upon too short after-periods. Nash and Benedict (149) found a very similar lag in the nitrogen excretion after a mixture of dextrose and urea in which the D:N ratio was 3.6 had been fed to phlorhizinized dogs. The subsequent D:N ratios in the urine were raised well above the control level for about 4 hours, and then depressed greatly for about 12 hours longer, before the original quotient was reëstablished. Thus approximately 16 hours were required for the whole series of readjustments to be accomplished. The construction placed by Gaebler and Murlin (74) upon these experiments, that the power of the kidney to eliminate urea is impaired by phlorhizin, is not justified by the facts. It is obvious that interpretation of feeding experiments should be based upon sufficient after-periods. The bearing of these relations upon calorimetric experiments has already been indicated.

2. The energy quota of protein metabolism: It has been shown by Lusk and his pupils (cf., for example, 158) that the protein catabolism in phlorhizin diabetes is increased very greatly above the starvation requirement. This increase is not so large in herbivorous animals as in the dog, which yields a higher D:N ratio. Ringer (161) has analyzed the whole protein metabolism of the phlorhizinized organism into three components: 1. The "minimal nitrogen requirement," which corresponds to Rubner's "wear and tear quota." 2. The "dextrose nitrogen," which represents the amount of protein catabolized in excess of the "minimal nitrogen requirement" in case of specific nitrogen hunger and in the absence of carbohydrate from the diet. This factor is brought into operation by the associated hypoglycemia, and is absent in pancreatic diabetes. It may be the most considerable of the three components, and may be spared only by a sufficient concentration of carbohydrate in the tissues. 3. The "complementary nitrogen" which represents the amount of protein catabolized for dynamogenetic purposes in cases of starvation in excess of "1" and "2," or when large quantities of protein are added to the diet. The nitrogen of this fraction may be spared by any foodstuff. It has been confirmed repeatedly that the "dextrose nitrogen" quota may be spared by a mere increase in the concentration of carbohydrate in the organism, although none of

the carbohydrate is burned. Janney (101) has postulated that the sparing action of dextrose on protein metabolism, which cannot be accounted for adequately on a dynamic basis, may be due to protein repair and synthesis from intermediary products of carbohydrate metabolism.

Lusk (126) has shown that the heat production of the fasting, phlorhizinized dog may increase to as much as 70 per cent above the basal. Such tremendous increases in metabolism are attributed by Lusk to the specific dynamic action of the three- to five-fold increase above the normal in the quantity of amino-acids metabolized. The direct stimulus to metabolism is supposed to be provided by such intermediary products as glycollic acid or lactic acid, since it was found that glycocoll or alanine increases metabolism when given to phlorhizinized dogs, though neither is oxidized and the energy content of the substance is eliminated in the form of sugar and urea in the urine. Hári and Aszódi (88) claim that the increased protein destruction in phlorhizinized rats is associated with a reduced heat production, and consequently the increased heat production observed in dogs cannot depend upon the increased destruction of protein. These authors believe there is an effect of phlorhizin on the heat regulating centers which is independent of the heightened protein destruction. Lusk (125) has shown further, however, that the usual increase in heat production in phlorhizin diabetes does not occur after removal of the thyroid, for the reason that the protein metabolism does not then increase. Janney (101) has observed that the sparing action of sugar on the protein metabolism is increased by the additional feeding of minute doses of thyroid tissue.

3. Effect of work upon the protein metabolism: Lusk (129) considers it to be fully proved that muscular work does not increase the protein metabolism. In experiments with phlorhizinized dogs (123), which were made to run in a wheel, a rise in the protein metabolism, as indicated by the urinary nitrogen findings, accompanied the mechanical work only when extra carbohydrate was also eliminated. A completely deglycogenized dog showed no rise in the nitrogen elimination after traveling 1500 meters during an hour divided into alternating 5-minute work periods and 5-minute rest periods. The extra elimination of nitrogen following work by phlorhizinized dogs whose tissues still contain glycogen, is explained by Lusk on the basis of the experiments by Murlin (143), who demonstrated a considerable retention of glycocoll when this was ingested with carbohydrate,—a retention which, however, was not permanent but depended upon the presence of the carbohy-

drate. Thus the removal of a rest of glycogen by work, according to Lusk, would bring about an elimination of nitrogen formerly belonging to compounds loosely combined with glycogen.

In some unpublished experiments (1922) the present author obtained results which confirm those just described for Lusk. The dogs were fasting and completely phlorhizinized, but no additional measures had been employed to deglycogenize the animals. The work done represents distance traveled in a motor-driven wheel, in one uninterrupted period. The results may be summarized as follows:

PERIOD	DAY OF DIABETES	DISTANCE TRAVELED IN METERS	DEXTROSE PER HOUR	NITROGEN PER HOUR	D:N
		Dog A-33			
1:45 a.m. to 8:45 a.m.			1.19	0.32	3.70
3:05 p.m.			1.21	0.32	3.76
5:15 p.m.				Urine lost	
7:05 p.m.	4	2160, 5:15–5:40 p.m.	1.76	0.35	5.02
8:15 p.m.			1.30	0.30	4.33
11:25 p.m.			1.15	0.30	3.78
Dog A-34. Average hourly excretion of N for control 24-hour period, 0.266 gram					
12:20 n. to 6:10 p.m.			1.05	0.266	3.95
9:50 p.m.	4	4400, 6:15–7:25 p.m.	1.67	0.297	5.60

It will be noted that in each instance there was a transient increase of about 10 per cent in the nitrogen elimination, but this coincided with a rather large excretion of extra sugar. In the light of the present knowledge of the glycogen storing capacity of the phorhizinized animal, it would seem plausible that the temporarily increased nitrogen metabolism noted in such experiments is a response to the stimulus of the further carbohydrate impoverishment of the tissues, and should be classified with Ringers's "dextrose nitrogen" quota.

In connection with the above the more recent work of Chambers and Milhorat (30) upon normal fasting dogs may be cited. After short fasting periods of 1 to 5 days insulin injections increased the nitrogen excretion. This finding accords with an observation by Nash (147). With longer fasting insulin produced no effect. When, however, carbohydrate was administered to an otherwise fasting animal insulin

produced the same increase in nitrogen excretion in the later stages as in the earlier days of the fast. Such findings support the suggestion by Lusk (above) of a loose combination between glycogen and nitrogen in the tissues. Chambers and Milhorat interpret their results as indicating a correlation of the insulin effect with the presence of carbohydrate reserves in the body rather than with a calling forth of reserve protein to counteract the insulin after depletion of the carbohydrate stores. In exercise experiments on fasting dogs these same authors found an increased nitrogen elimination during the early part of the fast, but not in later periods; and not in the earlier periods if sufficient carbohydrate was supplied.

Opposed to the foregoing is the opinion of Cathcart (25) who has recently summarized the literature concerning the influence of muscle work on protein metabolism. Cathcart asserts that the accumulated evidence points in unmistakable fashion to the conclusion that muscle activity does increase, if only in small degree, the metabolism of protein and the nitrogen output.

4. The fat metabolism: It is long since a matter of general observation and experimental demonstration that fat may be formed from carbohydrate, and hence from protein, in the animal organism. The striking paucity of experimental evidence on the mechanism of a process so surely known to occur emphasizes the service which the diabetic animal has rendered to the study of the intermediary metabolism of substances whose reaction products are excreted for ready demonstration, and not elusively hidden away in the tissues. The intermediate stages of fat synthesis are still for speculation only. If, as assumed, glyceric aldehyde is an early degradation product of carbohydrate, the derivation of the glycerol constituent of the fat is reasonably assured. Lusk (129) believes that the synthesis of the fatty acid probably involves the condensation of acetaldehyde molecules derived from methylglyoxal, as postulated by Magnus-Levy (131). Haehn and Kinntof (87) have recently supported this view with the observation that when yeast cells are placed in phosphate-buffered solutions of acetaldehyde fat droplets are formed. On the other hand, Maclean and Hoffert (130) conclude from a study of the carbohydrate and fat metabolism of yeast that the evidence is against the view that either acetaldehyde or pyruvic acid is an intermediate stage between the hexose molecule and the fatty acid. The deduction is made by these authors that acetaldehyde is first condensed to hexose and the latter directly condensed to form higher fatty acids without passing through a fatty aldehyde stage; the

lower fatty acids are assumed to be degradation products of the higher and not intermediates in their synthesis.

It would appear that a question of the reverse process, the formation of carbohydrate from fat, would be decided readily and positively. Lusk (124) has summarized in admirable manner the evidence against the view that carbohydrate may be formed from fat. It is difficult indeed to reconcile the argument cited by Lusk with any other conclusion. When fat feeding even in excess of the total energy requirement is without effect upon the D:N ratios of phlorhizinized animals, or when an amount of work capable of more than doubling the fat metabolism has no effect whatever on the sugar output of the completely diabetic organism, the proposition assumes the finality of fact. The view that adrenalin forces the conversion of fat into carbohydrate has been equally summarily disposed of, as already noted in these pages. Colwell (32) has recently added further confirmation on this point. Of course, as Lusk himself has recognized (123), the possibility is not excluded that a certain amount of sugar may be formed from the glycerol constituent of the fat. *A priori*, it would be expected that this should be so if the metabolism of the fat molecule is not as a unit but involves a splitting into glycerol and fatty acids. But positive evidence for even this degree of sugar formation from fat is signally lacking. This particular aspect of the problem is complicated by the high calorific value of fat and the relatively small percentage of the whole molecule contributed by glycerol. Takao (201), who fed starving, phlorhizinized dogs 100 grams of bacon fat or olive oil without affecting appreciably the D:N ratios, reports an absolute increase in the amount of urine sugar which is attributed to the glycerol of the fat. But it is not clear why the extra sugar arising from this source should have carried along with it into the urine the amount of nitrogen corresponding to the fixed D:N quotient.

With such an overwhelming body of evidence against the view that carbohydrate may come from fat, it is surprising to find the question still so vigorously debated. The fact that the contrary idea will not down testifies to the innate conviction that all chemical reactions are, or should be, reversible. Geelmuyden (77) has recently revived the conception that adrenalin causes an increased production of sugar from fat in the liver, and the acetone bodies are an intermediate stage along the way; thus there exists in fat migration no antagonism but a causal relation between sugar poverty of the liver and acetonuria. At this point, also, may be recalled the suggestion of Ringer and Frankel (170)

and Ringer (166) that aldehydes (possible intermediates in the carbohydrate or protein metabolism) may combine with b-hydroxybutyric acid, so changing its structural configuration as to convert it into a glucogenetic substance. Burns and Marks (24) in a study of the perfused liver found that livers free or nearly free from glycogen and diffusible substances produced sugar in amounts such that a conversion of fat to reducing sugar was indicated; adrenalin, however, had no obvious effect on the process. Wertheimer (214) finds that insulin causes fat to disappear from the liver of the phlorhizinized dog, and simultaneously glycogen makes its appearance. The author asserts that the only explanation is sugar must arise in some way from fat. Chaikoff, Macleod, Markowitz and Simpson (27) lean to the view that fat may produce carbohydrate, since they find the D:N ratios to be higher in fat than in lean depancreatized dogs. Markowitz (132) believes that the experiments upon the respiratory exchange and D:N ratios of depancreatized and phlorhizinized animals, which support the contention that endogenous fat cannot form carbohydrate, are not conclusive since the calculations are based on several unproven assumptions, chief of which is the inability of such animals to oxidize glucose. Brugsch, v. Exten and Horsters (21) interpret their findings with respect to sugar formation in starved phlorhizinized animals as indicating the derivation of sugar from fat. Clutterbuck and Raper (31) distilled the products of a reaction between acetoacetic acid or ester and hydrogen peroxide, and found that the distillate reduced Fehling's solution in the cold and gave an osazone. The experiment is interpreted as suggesting the possible derivation of carbohydrate from acetoacetic acid.

III. The clinical use of phlorhizin. While various attempts have been made from time to time to find some clinical use for phlorhizin, no important therapeutic or diagnostic application of the drug has been generally conceded. Perhaps the most persistent effort in this category has been to employ the glycosuric effect of phlorhizin in a differential diagnosis between normal and pathological kidneys. Lusk (124) has cited the conflicting and uncertain results reported for such methods, which are, apparently, no longer seriously employed.

Rosenberg (176) has claimed that diabetics show a much stronger phlorhizin reaction than normal subjects, and the glycosuria and hypoglycemia are prolonged and increased. With severe renal insufficiency and a rest-N increase above a certain level, the phlorhizin glycosuria falls to subnormal values or is entirely absent, while the blood sugar usually but not invariably rises.

Chabanier and Lobo-Onell (26) injected men with small doses of a dilute phlorhizin solution. No influence was detected upon the ratio blood urea: urine urea, although a pronounced glycosuria was present (6 to 36 per cent sugar).

Kamnitzer and Joseph (109) claim that 2.5 mgm. of phlorhizin injected subcutaneously regularly produces in pregnant women a significant glycosuria within one-half hour. In control experiments on 70 non-pregnant women, and 10 men, 63 of the women and all the men reacted negatively to the test. Therefore a negative glycosuria after 2.5 mgm. of phlorhizin excludes pregnancy.

Dünner and Mecklenburg (53) report that the injection of NaH_2PO_4 or Na_2HPO_4 represses the phlorhizin glycosuria.

Probably the most interesting and logical clinical application of phlorhizin was that undertaken by Benedict and Lewis (16) in the treatment of malignant tumors. The work was based on the idea that utilization of sugar plays an important part in the synthesis of new protoplasm. Forty rats were inoculated with sarcoma transplants, and placed upon a carbohydrate-free diet. Two-tenths gram of phlorhizin in olive oil was administered once in 2 to 3 days. Where the animal could survive the treatment for at least 10 days with complete diabetes there was retrogression and ultimate cure of the growth provided the latter at the time of beginning the treatment did not exceed 20×30 mm. A similar treatment was extended to one case of human malignancy. Wood and McLean (218) have criticised these results, claiming that the disappearance of tumors in such cases is due to spontaneous resorption and not to the diabetic state. Since Warburg has shown that the building up of carcinomatous tissue is at the expense of the cleavage of glycogen into lactic acid it would seem that phlorhizin has a rational indication in the experimental therapeutics of cancer.

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ARTERIAL HYPERTENSION AND HYPOTENSION AND THEIR CLINICAL SIGNIFICANCE

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I. INTRODUCTION. A review of the clinical significance of changes in arterial pressure is one of colossal magnitude from the point of view alone of the published literature referable to it. It would seem a truism that the less a subject is understood the more is written about it. This is natural as theories and counter-theories with hypothesis upon hypothesis are put forward to attempt to elucidate an unknown or but little understood phenomenon. Medical bibliography is so rich in publications on blood pressure from a clinical standpoint that it would be an almost impossible task to review and correlate them all. The writer therefore wishes to apologise for seeming neglect of many publications. On the other hand, critical contributions undertaken to explain pathological changes are relatively so few that the proper prospective has not been maintained.

It is the purpose of the present article to review as far as possible the observations on abnormal arterial blood pressure which are based on original investigations of the subject and to attempt to draw conclusions as to the clinical significance of abnormality of this function. It will be obvious that our knowledge of the underlying cause and of the processes whereby these changes in arterial function are brought about is quite meagre.

There was a tendency for many years to consider hypertension as a disease in itself. This is not the case at present. It is now held to be but a sign of some more fundamental derangement of the biological functions and it has a clinical significance only insofar as it can be used to guide diagnosis and prognosis in disease. Therapeutic attempts to reduce or increase pathological variations in arterial pressure have been tended up to the present with doubtful success and have frequently been prompted by less wisdom. In those conditions where our knowledge has afforded us an understanding of the method of production of such a change, its correction, without at the same time striking at the cause, has been followed by disastrous results.

Methods. "Hard" and "soft" pulses have long been identified with certain diseases. The first method of determining changes in arterial pressure was by digital palpation of the radial pulse without the assistance of other mechanical means, and although this method was crude still the knowledge so obtained served as an important basis for future work. The introduction by Riva Rocci (1) in 1896 of a mechanical method with a manometer and an armlet for compression of the artery was the first step toward accurate measurements of systolic pressure in human disease. This method was not without its fallacies which were of mechanical detail as, for instance, the use of armlets of different widths. The work of Recklinghausen led to the adoption of an armlet of standard size. The determination of the systolic pressure revealed only part of the story, which was more or less completed when the oscillatory method of determining both the systolic and diastolic pressures was introduced. The next step forward was the development of the auscultatory technique by Korotkoff (2). This has now, on this Continent at least, superseded all other clinical methods for the determination of both systolic and diastolic arterial pressures. The discussion regarding the virtues of the different methods (oscillatory, ausculatory and vibratory) will not be entered into here. Under certain modifying circumstances one or other may have its advantages, but on the whole the auscultatory method has received the most widespread recognition and adoption.

As arterial blood pressures are recorded in millimetres of mercury, the mercury manometer must necessarily be the standard against which all other forms should be standardized. From time to time new types of instruments are brought forward. The modifications are usually those of convenience rather than of principle and it would serve no useful purpose to discuss them here.

It would be well, however, to outline briefly the criteria upon which the systolic and diastolic pressures are determined by the auscultatory method. An armlet of standard width is used (approximately 13 cm. wide when flat). The recording apparatus may be an aneroid or other manometer provided it has been compared at repeated intervals with a mercury standard. The latter, however, is the best for accurate work. The sounds produced by pressure of the vessels are heard by placing the bell of a stethoscope over the artery peripheral to the armlet. Five different phases or qualities of sound are heard as the pressure in the armlet is raised and lowered. At the maximum pressure a clear sound is heard. This disappears rather suddenly as the pressure is further

raised and the point of its disappearance is taken to be the maximal systolic pressure. As the pressure is then lowered this sound reappears and, on further reduction of pressure, becomes muffled but at a lower level it reacquires a loud snapping quality which gradually increases, but rather suddenly changes to a muffled whiff. This point is taken to indicate the level of the diastolic pressure. A few millimeters pressure below this the sound usually disappears completely. The point where the sounds disappear at the maximal or systolic pressure is not at all difficult to determine with consistent accuracy by different observers. In regard to the diastolic pressure, however, there has been some difference of opinion as to whether it should be recorded at the point where the clear snapping sound suddenly becomes muffled or where the sounds completely disappear. Without entering into a discussion of this argument, it may be stated that the consensus of opinion and custom based on experimental data is to take the diastolic reading at the level where the snapping sound changes to the muffled whiff. In certain types of cases to be referred to later it is impossible to do this, as a snapping sound persists even when the armlet is removed. This phenomenon is always associated with other evidence of a great increase in the pulse pressure, which is the difference between the systolic and diastolic pressure. It is sometimes well to supplement the auscultatory method with the tactile method in determining the systolic pressure, while the vibratory method may be employed to check the diastolic estimation. This is done by placing the finger over the artery just distal to the stethoscope and detecting the vibration occurring when the pressure approaches the diastolic level.

The relative values of the systolic, diastolic and pulse pressures is of great importance. The ratio of 3–2–1 is usually considered as the normal. This has undoubtedly been so considered because it is the ratio which is found most commonly in young adults when the systolic pressure is about 120 mm. Hg and the diastolic 80 mm. Hg, but this ratio does not hold good in otherwise equally normal people who may have arterial pressures above or below these readings. As will be shown below, the level of so-called normal readings cover a wide range. It may betaken as a general rule that as the systolic pressure is low, so the ratio changes to the order of 5–3–2. The pulse pressure in this example is more than one-half of the diastolic and one-third of the systolic pressure. A similar change in the ratio occurs with higher systolic pressures which are to be considered within normal limits, while the changes produced by physical exercise show much more striking differences.

The systolic pressure represents the maximum intra-arterial pressure at the end of cardiac systole. It therefore gives some indication of the amount of blood expelled into the arterial tree at each systole, plus the peripheral resistance. The diastolic pressure represents the intra-arterial pressure during the diastolic phase of the cardiac cycle. It indicates the minimum pressure to which the arterial wall is constantly subjected and also the initial pressure which the left ventricle has to overcome at the beginning of systole before it can expel its contents into the arterial system.

Average normal values. Since systolic blood pressure determinations have become part of the routine examination for life insurance, statistics based upon large numbers of presumably healthy persons have been accumulated. The work of van Wagenen (3) MacKenzie (4), Fisher (6) Rogers and Hunter (5), Goepp (7), Symonds (8) and others forms the basis for our present knowledge of the systolic arterial pressures in average or normal people. It may be stated that their figures agree closely with each other, and that from the age of 15 years to 66 years the systolic pressures show a progressive increase from 119 mm. to 139 mm. In regard to the difference between men and women, it would appear to hold in large numbers of cases that the systolic arterial pressure was a few millimeters lower in women than in men up to the age of forty, and then tended to rise relatively rapidly to a few millimeters above that of men. This was particularly evident when "build" was compared, as was done by Symonds (8).

These averages must not be too rigidly applied in clinical medicine where a particular individual is dealt with, as it was found that there was a considerable variation in otherwise apparently healthy people. It would appear that a variation of 15 mm. above or below the average may be considered as still within the normal limits. In other words, that the normal systolic arterial pressure for men may be taken to be within the range of 104 mm. to 134 mm. at 15 years, gradually increasing with age to 124 to 154 mm. at 65 years. The variations from the average in women is practically the same.

Statistics on the diastolic arterial pressure are fewer than on the systolic pressure and the same reliance cannot be placed upon them. Symonds (8) has carried out an extensive analysis of diastolic pressure estimations. He took as the index of the diastolic pressure by the auscultatory method "the very end of the fourth phase, practically just before the beginning of the silence." This period of muffled sound extends, as MacKenzie (4) points out, over about 2 to 6 mm. Hg in 75

per cent of the cases he examined. Therefore, this must be taken into consideration when these results are compared with those obtained when the diastolic pressure is taken at the end of the snapping or third sound. Symonds found the diastolic pressure for all "builds" to vary from 79.5 mm. Hg at 15 to 19 years to 86.9 mm. Hg in persons over 60 years. MacKenzie (4) analysed the findings in 5,018 cases and found that the average diastolic pressure from 15 to 39 years was 89 mm. and from 40 to 66 years it was 93 mm. The average variations in these intervals was in the first series from 88 to 92 and in the second from 91 to 98. MacKenzie draws attention to the fact that with each succeeding calendar year (from 1912 to 1915) the average diastolic pressure became lower, indicating, in his opinion, an increasing expertness of the examiners. It is important to note that the variations from the average high to the average low readings in his series ranged from 101 mm. to 81 mm. or a variation of 20 mm. Stocks and Karn (9) have made an exhaustive study of arterial blood pressure, taking into consideration the many daily factors which may modify it. Those who are interested in this subject, particularly with reference to the variations and changes of blood pressure in early life, would be well repaid by studying their work in detail. The writer will frequently refer to their conclusions in the following sections.

It must, however, be borne in mind that the vast numbers upon which the averages quoted above were based, were obtained in the most part from insurance company statistics. It would not be altogether fair to conclude that all apparantly healthy people of these ages would fall into these values of blood pressure. It is frequently stated that many cases are not included in these statistics because the deviation of the observed blood pressure was beyond the range of what was considered wise to accept as a good insurance risk. It will be with cases such as these that the present review will be chiefly concerned. The field of medicine does not only lie where the average is considered to be normal but variants have to be assessed from the point of view that such variations *may* have a pathological significance, and to determine what this variant *may* mean in the future of the individual.

The pulse pressure, as already stated, is the difference between the diastolic and the systolic pressures. It will vary, therefore, as these two pressures either approach or deviate from each other. It may be described as the extra arterial pressure developed with each cardiac systole to carry on the circulation. Stocks and Karn (9) have correlated the published statistics of pulse pressures up to the time of their publica-

tion. In the chart they publish it is graphically demonstrated that the pulse pressure increases from 5 years of age up to between 17 and 18 years, where a peak is reached. After this it declines to 21 years, when a slow but steady increase continues to 37 years.

II. AVERAGE VARIATION DURING THE LIFE CYCLE. The significance of variations of arterial blood pressure depends in its final estimate upon the deviation from the average normal under any given conditions. It would be well, therefore, to review briefly the variations which occur during the life cycle of the human race.

Infancy. A number of interesting studies have been made of the blood pressure in infancy, particularly by Sietz and Becker (14), Lienê and Buiet (13), Balard (12), Papris (10), Nizzoli (11), Rucher and Connell (62) and Reis and Chaloupka (63). The general findings have been that at birth in a viable infant the systolic blood pressure varies between 20 to 60 mm. Hg with an average of 40 mm. At the end of the first week it is about 60 mm., at the end of a fortnight 70 mm., and at the end of the first month about 80 mm. Hg. These values however would appear to be dependent upon the weight and general physical as well as circulatory vigour of the infant. Balard (12) emphasizes the importance of the systolic blood pressure as an indication of the general vitality and progress of its physical development. From the end of the first year the systolic and diastolic pressure slowly but steadily increases throughout the years of childhood until at the age of 12 the systolic pressure has reached on the average about 100 mm. It is important to note at this time (in view of further discussion of hereditary influence on hypertension) that no cases are on record where an unusual and spontaneous increase in blood pressure was found.

Childhood and adolescence. Whereas during the period of childhood the blood pressures of boys and girls run more or less parallel, on the advent of adolescence a distinct change is found. The change occurs sooner in girls than in boys. Faber and James (169) have made a complete statistical study of arterial pressure in children and give important standards and variations. Burlage (15) who reviews past work on the subject, came to the conclusion that there was a progressive increase of the systolic blood pressure to the age of 9, after which the acceleration became more rapid, but particularly so during the fourteenth and fifteenth years. Then there was a slight fall to the eighteenth year, after which it resumed a slow but steady rise during the subsequent age periods. In boys the rise is somewhat more uniform as far as the systolic pressure is concerned, as shown by Stocks and Karn (9), but the

maximum is not attained until the age of 17 or 18, after which there is no decline as found in girls.

The diastolic pressure shows more striking changes, there being a rapid increase between the ages of 13 and 15 in girls and between the ages of 17 and 22 in boys (figs. 1 and 2).

The variations in the pulse pressure accentuate these differences, as will be seen in figures 1 and 2.

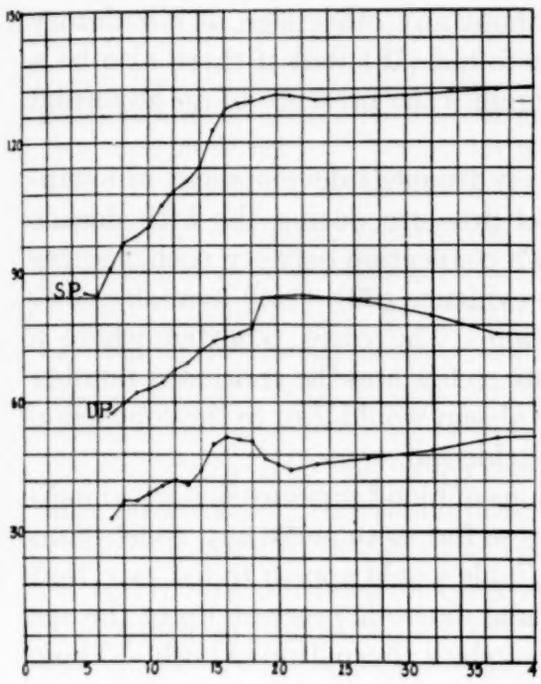

Fig. 1

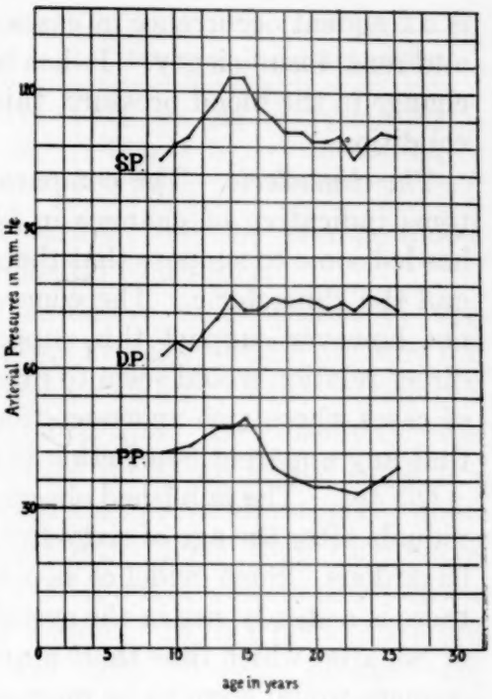

Fig. 2

Fig. 1. Blood pressure curves in males. Upper curve, systolic blood pressure; middle curve, diastolic pressure; lower curve, pulse pressure. Ordinates, millimetres Hg; abscissae, years. (After Stocks and Karn: Cambridge Univ. Press, 1924.)

Fig. 2. Blood pressure curves in females. Ordinates, millimetres Hg; abscissae, are in years.

Pregnancy. The consensus of opinion would indicate that normal pregnancy is not accompanied by any pronounced change in blood pressure. It may be taken as a general rule (Litzenberg, 17; Schulze, 27; Hinselmann, 28) that the systolic blood pressure slowly increases after the fifth month of gestation. This in normal cases does not assume unusual proportions and on the average is about 10 mm. After deliv-

ery there is usually a slight drop in the systolic pressure amounting to from 10 to 20 mm. but sometimes as much as 50 mm., but never sufficiently pronounced to produce syncope in normal cases. This is in striking contrast to what occurs in certain pathological conditions to be referred to later. The diastolic pressure does not show as significant changes as does the systolic pressure. The data of pulse pressure are so scant as to preclude of any definite conclusions being drawn.

The development of edema in pregnancy during the latter months is a frequent occurrence in cases without any other sign or circulatory and renal insufficiency. It has been found (18) that if there also be a change in the blood pressure, this signifies the presence of an abnormal condition.

The climacteric. The comparatively frequent development of symptoms indicative of changes in blood pressure during the fifth decade has led some to suppose that there is a connection between such changes and the climacteric. The concrete evidence (29), (150) available does not however support this supposition. The cases reported where a direct relation would seem to exist are so few and the enormous number of cases where such an association is absent would lead to the conclusion that any apparent connection is coincidental.

Old age. The published observations of blood pressure in normal individuals after the age of sixty-five are so few as to make any conclusions hazardous. Such evidence as is available would appear to indicate that there is a steady rise in the systolic and diastolic pressure up to the age of 85, after which time there appears to be a sharp drop in both. These changes would seem to be more striking in women than in men.

Racial differences. Such observations as are available would indicate that the systolic blood pressure is higher in Anglo-Saxons of British or American birth than in East Indians (9) and Chinese (19), (20). The differences in diastolic pressure are not so pronounced. Therefore, there is generally a higher pulse pressure in the Europeans than there is in the other races mentioned. It must be realized, however, that the numbers available are not sufficiently numerous to allow of too dogmatic conclusions being drawn.

III. Average variations due to environmental conditions. *Basal state.* The determinations of blood pressure outlined above have practically all been taken under ordinary day time conditions. These are, on the whole, those in which the vast majority of clinical observations have been made and should constitute the average standard. On the other hand, there are deviations from this standard which

are at the same time normal and must be considered in their relation to this so-called average condition. In comparison with the so-called average condition there is the basal state in which no exercise or other disturbing factor has intervened from the sleeping state, or what may be considered as the absolute resting period, barring incidental disturbances, such as dreams. Adis (30) has compared the ordinary day time blood pressure with those of basal conditions and has found the following differences as an average:

	SYSTOLIC	DIASTOLIC	PULSE PRESSURE
Basal pressures	99 mm. Hg	71 mm. Hg	28 mm. Hg
Day-time pressures	127 mm. Hg	78 mm. Hg	50 mm. Hg

It is quite evident from these observations that the average blood pressures vary under different environmental conditions.

Sleep. Müller (21) has made an extensive investigation of the blood pressure during sleep. He found the average systolic pressure for men at all ages to be 94 mm. and for women 88 mm., while in children between the ages of 3 and 14 it averaged 82 mm. He considered this constant drop to be due to the relaxation of the tonus of the small peripheral arteries. Individual differences found in the day-time systolic pressure seemed to be eliminated during sleep. Thus, these differences seemed to be conditional on variation in the tonus of these arteries which were probably influenced by external stimuli. Müller found that the sleeping systolic pressure tended to rise after 45 years of age. He believed that this was the true level of the systolic pressure and that the day time pressure was influenced by factors which could not be determined. He also came to the conclusion that their action could not be estimated in either the normal or the abnormal until sleep was induced and the systolic pressure then taken and compared with the waking pressure. In cases with increased arterial tension he found the fall during sleep was less than normal and that this was in proportion to the severity of the associated signs and symptoms. Further, that the amount of nocturnal urinary excretion approximated the day-time amount in direct ratio as the sleeping blood pressure approached the waking pressure.

Katsch and Pansdorf (23) and Blume (22) repeated this work and came to the same general conclusions. Since then Landis (31) has reinvestigated the question and has made observations on both the systolic and diastolic pressures and has found a decrease in both during sleep as

well as a reduction in the pulse pressure. He carried the enquiry farther and found that the increase on awakening depended upon the manner in which this was done. A sudden awakening produced a sudden increase, while if it were quiet and gradual the increase was slower and less pronounced. Similar results were found by Campbell and Blankenhorn (58).

Hypnosis. Lenk (32) has made some interesting observations upon the effect of suggestion under hypnosis upon the systolic blood pressure. When under hypnosis without suggestion of any kind the systolic pressure approximates to that of sleep, but when he suggested any physical exertion, even without its being enacted, there was a prompt and pronounced increase in the systolic pressure. This could then be as promptly counteracted by an opposite suggestion.

Postural changes. The influence of change of posture, whether it be either active or passive, has been the subject of considerable controversy. This would appear to have arisen out of the fact that all apparently normal individuals do not react in the same manner. Schneider and Truesdell (26) have made an extensive investigation in 2,000 cases. They reviewed the past work on this subject and confirmed the chaotic state of this question. They came to the conclusion that opinion was in such disagreement because different classes of people reacted in different ways, whether the change of position was passive or active. They found that those cases with a low standing systolic pressure showed an increase in the recumbent position, while on the contrary a high standing pressure was reduced in the recumbent position. In addition to these two classes there was the third or intermediate group in whom the systolic pressure remained unchanged, irrespective of the position they assumed. In regard to the diastolic pressure, there was always an increase on standing which was in inverse ratio to the recumbent diastolic pressure.

It is suggested that an explanation of this difference in reaction may be found in the "habitus" of the individual, as investigated by Larimore (41) who found the systolic pressure higher in the sthenic type of person and conspicuously lower in the asthenic type. Rolleston (170) has reported the finding that during convalescence from fevers the systolic was higher in the recumbent than in the upright position.

Effect of work—physical and mental. There have been many records published of the effect of both physical and mental work upon the blood pressure. The majority, however, have dealt chiefly with the changes which occur after the exercise had been completed. Bowen

(33) published the first good account of the changes in blood pressure which are produced during the course of physical exercise. He found that there was a short primary increase in the systolic blood pressure, which was followed by a less sudden fall, and then by a more gradual decline, but the pressure did not return to normal level (fig. 3). The degree of these changes was dependent in a great measure upon the degree or severity of the exercise. Gillespie, Gibson and Murray (39) found that the rise in blood pressure was approximately proportional to the load but was not a direct line or relationship and that there were many individual variations.

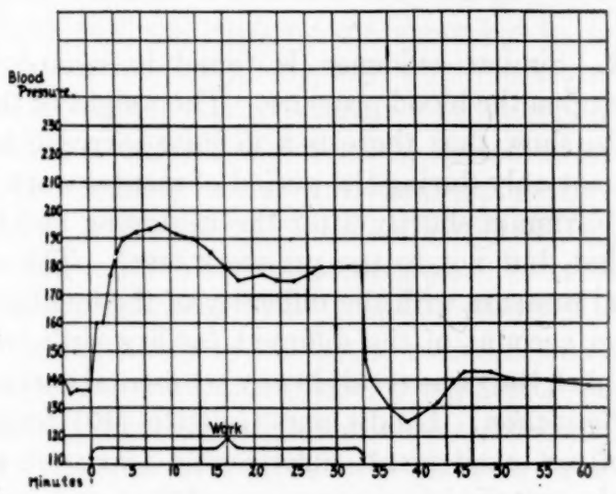

Fig. 3. Systolic blood pressure curve during rest, work and recovery period. Space between arrows is period of work. Ordinates, millimetres Hg; abscissae, minutes in time. (After Bowen: Amer. Journ. Physiol., 1904, xi, 59.)

The course of the blood pressure after exercise has been studied by many workers—Cotton, Rappart and Lewis (34), Smythe (35), Erlanger and Hooker (36), Lowsley (37), Schneider and Truesdell (26) and others. The findings are many times quite at variance, but it must be realized that the subjects examined offered many variables. The results are therefore governed by the training of the individual, the character, degree and duration of the exercise and the time after its completion when the readings were first made. It would seem to be proven that immediately on the cessation of the work there is a preliminary rise in the systolic pressure and then a fall, which may continue to below the normal resting pressure and then gradually return to the base line. The extent of these variations would seem to depend upon the degree of

exercise undertaken. There are also encountered frequent individual differences in degree rather than in type of change.

The diastolic pressure shows similar variations in different individuals. Immediately after a moderate exercise Schneider and Truesdell (26) found that in 46.6 per cent of cases it fell; in 22.8 per cent it rose; while in 32.6 per cent there was no change. Such results render it impossible to make any general rule to govern changes in diastolic pressure after exercise.

Schneider and Truesdell (26) found an increase of the pulse pressure much more frequently (76.7 per cent) during physical work, while in 13.3 per cent there was a decrease, and in 10 per cent there was no change.

Mental work. Similar evidence is found in regard to the effect of mental work upon the blood pressure. The weight of the experimental data goes to show that there is a definite increase in the systolic blood pressure not only during the period of mental work (38) but that it reaches its maximum shortly after the beginning and then tends to decline somewhat, but not to the pre-work level. The correlation of the rise of blood pressure with the difficulty of the mental work is hard to determine on account of the different facility with which different subjects accomplish the same result in any set mental exercise.

Emotional stimulation. Landis and Gullette (40) found that only the emotions of sex, excitement, surprise and fear were productive of any change in the systolic blood pressure and that even this change was of a temporary character. They consider that these variations were more probably due to physiological rather than to psychological causes.

Fatigue. Menard (24) and Briscons and Mercier (25) examined the blood pressure of French soldiers after active combat and during various stages of trench warfare. Their net result was to indicate that prolonged physical and mental stimulation sufficient to produce fatigue reduced the systolic and diastolic pressures but the former more than the latter, thus producing a reduction in the pulse pressure. With prolonged mental and physical rest all of these pressures tended to return to normal. They examined but a limited number and their results are suggestive rather than conclusive. However, the conditions more nearly approach the wear and strain of the ordinary round of life, the results of which the physician is called upon to treat, than do the short and more or less artificial experiments usually reported.

We have already referred to the finding that there is no consistent change in the blood pressure as found in the brachial artery on change

of position, either passive or active. The next point to be considered is whether the blood pressure remains constant in the different parts of the arterial tree under similar environmental conditions. In the first instance this must be considered in regard to the same arteries on each side. It has usually been considered and can easily be demonstrated that the rule is for the pressure to be equal on the two sides in animals if taken simultaneously with the same size of cannulae. In man there is certain evidence that this may not always be the case. Bowers in 1917 (16) found frequent differences between the two sides in elderly people. This was further emphasized by Cyriax in 1918 (43). His first observations led him to conclude that the pressure in one brachial artery was influenced one way or the other by an unilateral lesion. Subsequent observations (43), (44), (45) would indicate that this variation was not dependent upon traumatic or infectious lesions. The differences were not uniform and occurred in median lesions: thus they seemed to be independent of any unilateral disturbance which did not involve the limb examined. This difference in blood pressure Cyriax called "the differential blood pressure sign." Fischer (46) in 1924 also found differences in the blood pressure readings in the two arms when taken simultaneously but found no constant preponderance. The respiratory variations were, as a rule, of small degree, except in patients with hypertension where the differences were especially high.

It is usually taken as proven that the pressure decreases as the arteries become smaller. This is borne out by the observations of Bliedung (47) who found in man that whereas the pressure in the brachial artery was 115.6 mm., that in the central retinal artery was 105 mm. and in the smaller retinal arteries 83 mm. on the average. These differences have been confirmed in the cat by Duke-Elder (48) who found the mean pressures in the carotid 105.5 mm., ophthalmic artery 99.5 mm., in the retinal artery (first branching in the eye) 75.5 mm.

We now come to consider the variations in the blood pressure in different parts of the main arterial tree in the same and changed postural conditions. The earlier workers on this question obtained contradictory results. Hürthle (49) came to the conclusion that the mean pressure in the carotid artery in smaller animals was slightly higher than the femoral pressure; while Volkman (5) came to the opposite conclusion and Poiseville (51) and Dawson (52) found they were relatively constant.

The first important contribution on this subject in normal persons was reported by Hill and Flack (53) in 1909. They found that in the horizontal position the blood pressure in the brachial and femoral ar-

teries was practically identical in subjects with a normal vascular system. In the standing position, while the brachial pressure remained comparatively constant there was an increase in the femoral pressure. When these subjects were placed in the L posture, that is, the trunk and arms and head horizontal with the legs raised at right angles, the pressure in the brachial artery declined but little while that in the femoral artery fell much below that found in the horizontal position. A further change of posture to the head down, feet up vertical position, with the arms at the sides, produced a reduction in the pressure of both the femoral and brachial arteries, but more in the former. Hill (54) confirmed these observations in subsequent experiments and came to the conclusion that "they differ by the hydrostatic pressure of the column of blood which separates the points of measurement in the standing or inverted position." These observations in all their essential points were confirmed by Schott and Spatz (55) in 1924.

The workers on this subject, already mentioned, used the usual methods of determining arterial blood pressure in man, that is, the palpatory or auscultatory determination with a mercury or aerotonometer indicator. In 1925 Burdick, Clarke, Garlichs, Priestley and Richards (56) employed what they considered a more delicate photographic method to investigate this problem. By using this method they came to the conclusion that in the horizontal position in healthy young adults there was a difference between the brachial and femoral blood pressures. They found the difference at rest in the horizontal position to amount on the average to 38 mm. higher in femoral artery while immediately after exercise in the same position this difference had increased to 92 mm. In 1916 Gunning (57) carried out an important series of experiments in dogs in which he found that the mean pressures in different arteries (femoral, subclavian and carotid) differ considerably, usually from 8 to 40 mm. and in one case as much as 120 mm. He also found that the carotid pressure was definitely higher than the femoral pressure, which was quite contradictory to previous findings. These observations were made preliminary to the main object of the experiments, which was to determine the changes of blood pressure in different parts of the arterial tree produced by "adrenalin, nicotine and pituitrin." He found that all changes in systolic blood pressure were constant in the different vessels, irrespective of the preliminary differences. If the increase were an increase of 38 mm. in one artery, it was the same in others, irrespective of the original readings. Furthermore, it was found that this constancy was maintained in arteries of different sizes provided the bore of

the cannulae were constant. If, however, the cannulae were of different sizes, the changes bore an approximately direct ratio to their size.

Burdick and his co-workers claim that their results do not support Hill's (54) theory (hydrostatic) of the causation of a differential pressure, but are in agreement with Bazett's (57) theory of the importance of kinetic energy in its production. Such is the contradictory state of this subject at the present and in such we are compelled to leave it. Insofar as man is concerned, using the customary methods, the evidence is in favour of Hill's hydrostatic theory.

Altitude. Hunter and Rogers (5) in their survey of accepted insurance cases under standard plans could not detect any difference in the average systolic pressures of those who live habitually in the plains of North America and those who live in the Rocky Mountain region. In like manner they could not obtain any difference between the latitudes of the United States and Canada. Schneider and Sisco (59) found in men leading a comparatively inactive life at an altitude of 14,000 feet, that there was, as a rule, no change in the arterial pressure. Further work by Schneider and his co-workers demonstrated that there was sometimes a moderate rise in the resting systolic blood pressure immediately after arrival from a lower level. The most striking change was found on exercise. Under these conditions the rise in systolic pressure was more prompt than at a lower altitude and the maximum rise was greater. The increase in the diastolic pressure was comparatively slight. Both of these increases were most pronounced in those subject to mountain sickness, and further, it was found that with the development of acclimatization the changes on exercise became less pronounced, but did not return to the levels found at lower altitudes. Groszmann (61) found but slight change in the resting systolic pressure at 1550 metres shortly after arrival, but at 3460 metres there was a definite increase. She also made the important observation that this change could be rectified promptly by the inhalation of air enriched with oxygen. She found that on continued residence at this altitude the pressure inclined to return to the normal level as acclimatization developed.

VARIATIONS IN ARTERIAL BLOOD PRESSURE IN PATHOLOGICAL STATES. The normal variations of arterial blood pressure having been briefly reviewed we are now in a position to assess the significance of its changes in pathological conditions. Bright (62) in his classical communication dealing with "Cases and Observations Illustrative of Renal Disease Accompanied with Secretion of Albuminous Urine" first drew attention to the association of a cardio-vascular lesion with renal disease. Since

then both pathologists and clinicians have devoted much time and thought to its elucidation. The invention and improvements of instruments for the measurement of blood pressure have focussed attention upon the abnormal physiology of this function. In fact the rapid introduction of the sphygmomanometer into medical practice created a passionate enthusiasm for its investigation. After it was found that hypertension was not always associated with renal disease, this functional disturbance was elevated to the dignity of an entity of its own and *hypertension* with various qualifications leapt into the nosography of medicine. History repeats itself. Hypertension occupies about the same fatal position of finality of diagnosis today that *fever* as a disease entity occupied a century ago. As fever, tachycardia, tachypnea and other disturbances of function are but symptoms of local or general disease of a more profound character, so we must consider changes in blood pressure. Like also unto these disturbances, hypertension and hypotension in addition to being manifestations of abnormal processes, may lead in themselves to secondary pathological changes. Our task at the moment is to explain as far as possible the reason for these changes in blood pressure and their significance in the development and history of the pathological disturbances of which they form a part.

Before undertaking this task in detail it would be well to review how the blood pressure may be altered voluntarily. It has already been pointed out that increased work, either mental or physical, will lead to an increase in the systolic blood pressure with an increase in the pulse pressure. This normal response may be increased by such accessory factors as the oxygen want of high altitudes. This would appear to be a natural consequence resulting from a demand for an increased circulation to meet the requirements of the moment. An increase of cardiac output and of intra-arterial pressure are the two means whereby the general circulation rate is increased and upon them depends its regulation on the demand. This does not necessarily mean that they are both increased proportionately in every individual, although the general statement may be made that within certain limits the more active the metabolism the greater will be the cardiac output and the higher will be the blood pressur. This is well illustrated by the variations between work and sleep.

Another method whereby the blood pressure may be varied is through modifying the character of the peripheral circulation. A most striking example of this is to be found in the action of adrenalin. When injected intravenously there is a prompt increase of blood pressure. This

is brought about by the direct action of the drug upon the vasoconstrictor nerve endings, producing a constriction of the arteries and thus raising the peripheral resistance. The most pronounced action is to be seen experimentally in the vessels of the splanchnic area. Other substances have a somewhat similar effect on the blood pressure. Amongst these may be cited extract of the posterior lobe of the pituitary body, which acts on the musculature of the smaller vessels, producing vasoconstriction, and ergotoxine which acts in a manner similar to adrenalin. It will be seen from these examples that a constriction of the vascular bed increases the peripheral resistance and leads to a rise in blood pressure provided the muscular force of the myocardium is sufficiently powerful. The importance of this latter qualification will be referred to later.

If on the contrary there be a dilatation of the vascular bed, then a fall in blood pressure results. This is most easily demonstrated experimentally by cutting the great splanchnic nerve. This nerve is a vasoconstrictor and maintains the vascular tone in the blood vessels of the abdominal cavity. On removing its influence the vessels promptly dilate and a fall in blood pressure results. The blood pressure may be restored to its normal level by stimulation of the peripheral end of the cut nerve. It is presumed that a similar fall of arterial pressure may result from any influence in man which depresses this vasoconstrictor function. Pronounced reduction of the general arterial pressure may be induced by certain amines, such as histamine, which dilates the capillaries although to some extent constricting the arterioles. The net result, however, is a rapid reduction of the peripheral resistance and a fall in general arterial pressure which may be of fatal degree. The nitrites, the most important of which is amyl nitrite, also reduce the arterial pressure and in a manner somewhat antagonistic to adrenalin, namely, by dilating the arterioles.

There has been outlined above a law correlating systolic arterial pressure and metabolism, but another of greater importance may be enunciated here, namely, that the diastolic arterial pressure is in proportion to the degree of peripheral vascular resistance. After this brief summary, the next step is to attempt to explain the significance of changes of arterial pressure as they occur in pathological conditions.

IV. Diseases of the ductless glands. *Suprarenal glands.* The discovery by Oliver and Schäfer (64) of the profound effects of the extract of the suprarenal glands upon blood pressure in animals, led to the hope that in this reaction was to be found the explanation for the main-

tenance of blood pressure, and that disturbances of this glandular function would account for abnormalities in pressure. This was further emphasized by the occurrence of a low arterial pressure in Addison's disease, which was supposed to be due to a disturbance of the suprarenals. In order that this hypothesis might be proven, it was deemed necessary to demonstrate the presence of adrenalin in the blood plasma and, further, to show that this varied in amount with changes in the arterial pressure. It may be taken from the work of Stewart (66), Park (65), Hoskins and MacClure (67), Trendelenburg (68) and others that the amount of adrenalin in the general circulating blood is infinitesimal. Schäfer (69) sums up the evidence as follows:—"We cannot, therefore, assume that the normal tone of the vascular system depends on the presence of adrenalin in the blood, although that the maintenance of vascular tone is in some animals assisted in this manner is shown by the result of compressing the suprarenal vein."

Despite many assertions to the contrary, there appears to be little doubt that discharge of adrenalin may under some circumstances occur from the suprarenals in sufficient amount to produce some of the symptoms caused by intravenous injection of the autacoid. Nevertheless, such secretion is not indispensable for life, since none occurs after excision of one suprarenal and section of all the nerves passing to the other. This can be shown not only for the cat, in which the subject has been principally worked out, but also for the dog and monkey.

Although the experimental evidence in favour of adrenalin playing an important rôle in the maintenance of vascular tone is doubtful, yet under pathological conditions of the gland a change in vascular tone might be conceived. The most striking pathological processes where this might be effective would be where there were either an hypertrophy or a destruction of the gland.

Oppenheimer and Fishburg (70) have reviewed the subject of suprarenal tumors and hypertension. In regard to tumors of the medulla they have found only four cases of paragangliomas recorded with adequate observations of high blood pressure or the anatomical equivalent of hypertension. Although it is not infrequent to find diffuse and circumscribed (adenomatous) hyperplasia of the suprarenal cortex in cases of hypertension, the exact correlation of these two findings is not at all clear and there is no evidence that they are intimately connected one with the other. These authors have collected nine cases and report two of their own where cortical tumors were associated with pronounced hypertension. In all of the cases collected there was no evidence to

suggest the presence of renal damage as an etiological cause of the hypertension.

The best example of damage to the suprarenal which is associated with a loss of vascular tone and reduction in arterial pressure is to be found in Addison's disease. It is usually presumed that this disease is always associated with destruction of the suprarenals. Levine (71) found in a series of 684 typical cases of this disease that in 12 per cent there was no gross or ordinary microscopical changes in the suprarenals.

It is true that hypotension is a symptom closely associated with Addison's disease. But it should not be concluded therefore that its occurrence is a significant indication of deficiency of suprarenal function. Indeed, as the technique for the removal of the suprarenal glands has improved, the evidence in favour of adrenalin being an important factor in the maintenance of blood pressure in otherwise healthy animals has steadily become less conclusive.

The evidence in favour of the contention that adrenalin is always proceeding in sufficient quantities into the blood stream to maintain the tone of the blood vessels would indicate that the action of certain drugs may produce an increased activity of the suprarenals. The carefully controlled experiments of Asher (72) demonstrated that stimulation of the splanchnic nerves produced a pronounced rise of blood pressure which fails if the suprarenal veins are cut. There appears to be a reflex centre for the secretion of adrenalin in the fourth ventricle (73) subject to stimulation of the afferent nerves (74) or through stimuli coming from the higher nerve centres in the brain. The question whether emotional disturbances produce an increase of adrenalin secretion has been the subject of considerable debate amongst physiologists, but until this question is settled from an experimental point of view it cannot be given definite clinical significance. On the whole, the evidence is in favour of an increase of adrenalin secretion under excitation.

The effect of certain drugs upon the increased flow of adrenalin would seem to be quite definite. The more important of these are strychnine, nicotine, strophanthus and camphor. In the ordinary life of people at the present time the prolonged effect of nicotine would appear to be the most important.

Thyroid gland. The question of the influence of the thyroid secretion upon the blood pressure has attracted considerable attention, not only on account of its clinical importance but also through the divergent views which have been expressed. Hensen, Grass, Jackson and Federn

have reported an increase of the systolic pressure, while Gibson and Fränckel have reported no change. More recent observations have been made by Plummer (75) and Taussig (76) who have found an increased systolic and pulse pressure in the thyro-toxic cases. Troell (77) has confirmed these findings and found an increase of systolic pressure and pulse pressure to parallel the increase in the basal metabolic rate in cases of exophthalmic goitre. He also found a decrease in these blood pressures after successful operation. In general, it may be stated that there tends to be an increase in the systolic pressure in proportion to the duration and degree of toxicity. This would appear to depend more upon the duration, although both play an important part. Whether this increase be due to the influence of the thyrotoxicosis directly upon the vascular system, or indirectly, through making the normal influence of adrenalin more effective, is not at present definitely demonstrated. Plummer cautions against laying too much stress upon the association of hypertension and goitre. This is amply justified at this time when the inclination is unconsciously to consider hypertension as a disease and not as an associated phenomenon occurring with many pathological conditions.

Of more constant occurrence than changes in the systolic pressure is the relative decrease of the diastolic pressure and the increase of the pulse pressure. This is an almost constant finding in cases where there is an increase of thyroid function. It occurs during the early stages of the disease and is roughly in proportion to the severity of the toxicosis. The pulse assumes the well known collapsing character due to the same qualities as are present in the pulse of aortic insufficiency and other allied conditions. Whether this be a compensatory process to aid the increased blood flow required to meet the increased metabolism is the subject for other communications. Following the similarity of the quality of the blood pressure readings in thyrotoxicosis and aortic insufficiency, Taussig (76) has found that there is a like divergence between the arm and leg blood pressures in both these conditions, namely, that the systolic blood pressure in the leg is on the average 30 mm. higher than in the arm in the recumbent position. Likewise he found a conspicuous increase of the pulse pressure in the leg.

In cases where there is a deficiency of thyroid secretion it is usual to find a reduction in the systolic and pulse pressures. This was found by Willius and Haines in a study of 142 cases of this disease and they could not identify any particular organic cardiovascular lesion attributable to the deficiency (149). This, however, may not always be the

case. It has long been recognised, particularly before thyroid therapy was instituted, that arteriosclerosis was a frequent complication in myxedema. This subject has been reviewed by Fishberg (146) who points out that in spite of this hypertension was not the rule, but that it occasionally was reported and that thyroid administration sometimes produced a reduction of the hypertension. Blood pressure readings in myxedema are important in cases with circulation failure. Whereas in thyrotoxicosis circulatory failure usually occurs through disturbance of cardiac rhythm, or where severe and persistent hypertension places an extreme burden upon the cardiac function, in myxedema circulatory failure appears where the systolic pressure is normal or below, but the pulse pressure is also reduced. Whether this failure results from a myocardial degeneration due to metabolic deficiencies, or whether it results from diminished stimulation is not clear. The fact remains that in cases of myxedema where circulatory failure ensues, either as demonstrated by a congestive condition or by symptoms of angina pectoris, the administration of thyroid therapy should be undertaken with great caution. The increased metabolism which results will necessitate an increased blood flow which may precipitate a rapid circulatory failure with disastrous results.

Other ductless glands. In recent years many theories resting upon presumed functional and anatomical disturbances of various other ductless glands have been advanced to explain deviations from the normal blood pressure. This has been a fruitful source for many publications. It is impossible to review them all even if there were any warrant to do so. The main difficulty arises at the present time through the difficulty of subjecting the theories or conclusions to experimental proof. On the other hand, many clinical observations have foreshadowed important discoveries in the realms of physiology and pathology. It would appear unwise, therefore, to arbitrarily rule all such observations out of court, although they should be received with a reasonable degree of critical reserve. Engelbach (78) in 500 so-called "endocrine cases" found hypertension in 10 per cent. In 30 per cent of these there was what he described as pluri-glandular dyscrasias in which the principal gland involved could not be determined. Furthermore, there was a great variation in the disturbance of glandular function in these cases. Similar cases showed hypertension and hypotension. In fact it would be difficult to come to any clear cut association between presumed cause and effect. Zenope (79) reports a series of cases with so-called disturbance of the ovarian or testicular function. He claims to have found an

increase in the blood pressure with hypofunction of these glands, which he attributes to compensatory thyroid hypertrophy. The administration of ovarian or testicular extract corrected this increase of blood pressure. Where there was presumed evidence of increased gonad activity the blood pressure was low. Gutman (80) on the other hand attempts to place the blame for hypertension upon the pituitary gland. Holmes (120) in a large experience of definite pituitary disorders states that "in most cases of tumor of the hypothesis both the systolic and diastolic pressures are lower than normal." This is particularly so in the chromophobe adenomata associated with dystrophia adiposo-genitalis: here the systolic pressure does not rise above 100 mm. of mercury.

The supposition that deficiency of some (or perhaps all) of the ductless glands is conducive to a lowering of blood pressure has been arbitrarily adopted by many clinicians. In fact, the literature of the past few years contains serious articles in which different men claim that practically every known ductless gland is the cause of either an increase or a decrease of blood pressure. The claims are so fantastic and the evidence so scanty that one feels it is hopeles to expect critical judgment or opinion in clinical medicine.

It may be stated that until more critical clinical and experimental evidence is forthcoming, the clinical significance of changes in blood pressure in diseases of the ductless glands may be disregarded on the whole, except in the cases of thyroid disturbances and *possibly*, in a guarded fashion, those of the suprarenal gland.

V. Disturbances of nutrition. It is important to determine whether there is an association between the physical development and the blood pressure in otherwise normal individuals. Dunham (82) made a study of the relationship between age, body weight and blood pressure in 8,645 healthy army officers: all cases with any physical defect had been eliminated. He found in those with overweight that there was a distinct increase in both the systolic and diastolic blood pressure over the average for the age, while in the underweight groups he found the systolic and diastolic pressures were on the lower limits of the average variation. This corroborated the earlier work of Hunter and Rogers (83), who made an analysis of 62,000 blood pressure readings in men and 5,000 in women. Their study clearly demonstrated that the blood pressure is lower than the average amongst those who are underweight and higher than the average in those who are overweight. It would therefore appear that there was a direct relationship between blood pressure readings and obesity.

Aubertin and Coursier (84) made a study of the blood pressure records in 70 obese people, who were mostly bed-ridden in an institution, and compared these findings with 24 in private practice who led an active life but in whom the obesity index was the same. This index they obtained by subtracting the metric height from the metric weight. The result of their observations would indicate that a sedentary life and a poorly balanced, excessively carbohydrate diet are conducive to obesity and an increased blood pressure. This, however, did not occur in every case and they made every effort to eliminate other causes such as renal and arterial disease. In the first group there was a normal pressure in only 10 per cent of the cases as compared with 62.5 per cent in the more active individuals. They reject the assumption that obesity in itself can cause an increase in blood pressure, but attribute both to a common but unknown cause. Similar observations have been made by many clinicians.

Rose (86) reported a remarkable decline of hypertension in cases of obesity in whom reduction had been accomplished through dietetic treatment and he further claimed that normal blood pressure was maintained if a properly balanced diet was continued. Terry (92) substantiated these findings by a study of 63 cases of obesity. He concluded that the majority of fat women who seek medical attention had hypertension which was usually without findings suggestive of nephritis, diabetes or syphilis. He found that on a high protein, low calory diet there was a decrease of weight along with a lowering of the blood pressure which frequently relieved the chief complaints. Petrazzini (85) advances the theory that the increased arterial pressure occurring with obesity is due to an interference with the entrance of blood into the skull on account of the accumulation of fat preventing the elastic play of the spinal dura. Such explanations have not been able of proof by experimental means, however, and there yet remains to be demonstrated a reasonable explanation of the association of these two pathological findings.

The association of obesity and hyperglycemia and hypertension has been pointed out by a number of other authors. O'Hare (87) reported 25 cases of hyperglycemia and hypertension. That these individuals might have been suffering from an early stage of diabetes he did not deny, but drew the analogy between early interference with the carbohydrate function and the interference with the renal function, which occurs in so many of these cases. Herrick (147) confirmed these findings and reported a series of cases with hypertension, hyperglycemia,

obesity and arteriosclerosis, which he held constituted a definite clinical group, and claimed that it was rare to find hyperglycemia in a thin person with hypertension. Hitzenberger and Richter-Quittner (88) report the blood sugar in 38 cases of high blood pressure and claim that hyperglycemia is the rule with both primary and secondary vascular hypertonia, and maintain that this hyperglycemia is different to that in diabetes in that it is independent of the diet and is evidently not due to a disturbance in assimilation but, they claim, to a permanent overproduction. On the other hand, Härle (89) and Kahler (93) were unable to discover any regular connection between the level of the blood pressure and the amount of sugar in the blood. Mohler (90) has made a study of 46 cases with glycosuria and a systolic blood pressure of more than 150 mm. Forty-five of these were distinctly overweight and thirty-six of them reported that they had weighed more than 200 pounds at some period in their lives. The ages varied from 30 to 70 years. Sixteen of them could be classified as having fully developed diabetes, while in only twelve were albumen and casts to be found in the urine. It might be claimed that all of Mohler's cases were potentially diabetics, although there would seem to be a reasonable body of opinion which considers that there is a difference between those cases of primary diabetes mellitus and those associated with hypertension. Katz-Klein (91) found that the diabetes associated with hypertension was, on the whole, milder than the type associated with normal blood pressure and, further, that the changes in the blood sugar and blood pressure in the course of treatment were by no means parallel.

Weinberger and Holzman have reported a series of cases which they believe indicate that large doses of insulin may reduce blood pressure irrespective of the level of the blood sugar. They suggest that this is brought about by the antagonistic action of insulin and adrenalin. Klemperer and Strisower (120) found in cases of diabetes with a raised blood pressure, a decrease in blood pressure following the subcutaneous injection of 10 units of insulin. This reduction was gradual and reached its lowest stage in about two hours. After this the blood pressure rose and reached its former level after some hours. The maximum decrease in blood pressure was from 20 per cent to 39 per cent. In cases of diabetics with normal blood pressure they observed a decrease in blood pressure of 5 per cent to 11 per cent after a like amount of insulin. In animal experiments the intravenous injection of large doses of insulin caused no decrease in the carotid pressure. In spite of a previous dose of insulin, adrenalin administered intravenously caused the characteris-

tic short-lived rise in blood pressure. It seemed strange that in normal rabbits no decrease in pressure was noticed after insulin injections, in spite of the fact that the blood sugar dropped from 0.12 to 0.024. Although they are not yet in a position to put forward an explanation of their findings, they suggest that the observations are not without theoretical and practical interest. Theoretically important is the possibility that the results may indicate an hitherto unknown factor in the regulation of the blood pressure mechanism. The importance of these observations must await further investigation.

It was considered for many years that a high protein diet had a definite influence on blood pressure. This was borne out by the observations of Goodall (94) who found a distinct drop in blood pressure in cases of chronic interstitial nephritis on a low protein diet. These results, however, were not conclusive that a high protein diet in itself had any influence on blood pressure independently of any action it might have in removing the cause of blood pressure in chronic renal disease. Mosenthal (95) made careful observations on this point in a number of cases and came to the conclusion that it is exceptional for a low protein diet to diminish the blood pressure, or a high protein diet to raise it. He suggests that the basis of the impression that a low protein diet affects blood pressure rests upon the report of Benedict (96) and his collaborators, who demonstrated that by under-feeding, the blood pressure of healthy, young male adults could be distinctly reduced. These observations agree with the general finding—that people who are underweight have, as a rule, a blood pressure below the average normal. This subject has been further studied by Strause and Kelman (97) who made careful observations on eleven cases with hypertension, due to different causes, and came to the conclusion that in patients with hypertension and, at the most, a slight impairment of renal function, variations in blood pressure did not bear a direct relation to the intake of protein food.

It may be taken as the consensus of opinion, based upon experimental evidence, that protein intake has no direct effect upon blood pressure.

The effect of the intake of food and water upon blood pressure has been investigated by Tolubekewa and Pawlowskaja (98). They found an initial increase in the blood pressure after meals, which was later followed by a lowering, which they presumed to be caused by the dilatation of the abdominal vessels. The changes were slight in healthy individuals and pronounced in hypertension.

A number of workers have determined the effect of the ingestion of a

moderate amount of fluid. Engelen (99) found that after drinking one or two bottles of beer there was no constant effect on either the systolic or diastolic blood pressure. Dorner (100) investigated the effect on blood pressure before, and one and two hours after, the ingestion of 1½ litres of water in cases of nephritis and healthy individuals. In the normal subjects there was no appreciable increase of the blood pressure, but in acute nephritis the blood pressure rose as with a true hydremic plethora, which could be combatted by restriction of water intake and a dry diet. This increase of blood pressure occurred even when the arterial function was already above normal. He found that this could be reduced by an infusion into the vein of 200 cc. of physiological salt solution, but that further infusions would raise it. In cases of nephrosis there is little evidence of hydremia and the blood would even become concentrated from the flow of water in consequence of the "freshet." In cases where there was arteriosclerosis of the vessels, a large intake of water appeared to raise the blood pressure but water restriction seldom led to any reduction.

Miller and Williams (101) found in patients with hypertension and presumably chronic interstitial nephritis, that the ingestion of a large amount of fluid would cause a very decided increase in blood pressure. In one instance they produced an increase of blood pressure from 190 to 280 mm. with an increase of weight from 124 to 142 pounds. This was apparently directly due to the amount of water consumed. It may be concluded, therefore, that where there is interference with the renal function, the ingestion of fluid may produce an increase of blood pressure, but this would appear to be in inverse ratio to the rapidity with which the kidney gets rid of the excess fluid.

For twenty years there has been considerable discussion as to whether there was a relationship between the retention of chlorides and elevation of blood pressure. The French school, led by Ambard (138), Combe (139), Lanfer (140) and others claimed that there was, while German workers (chiefly from Krehl's clinic) Loeb (141), Brodski (142) and Löwenstein (143), produced evidence to the contrary. Allen (144) (160) investigated the problem and came to the conclusion that the restriction of salt and water reduced the systolic and diastolic pressures in cases of essential and renal hypertension. His results have been confirmed by Houghton (145) and Calvert (102). On the contrary, O'Hare and Walker (151) carried out prolonged experiments on the effects of a salt-free diet on hypertension. They came to the conclusion that the extremely low salt intake advocated for the treatment of

hypertension did not offer any special advantage over the older, less rigid restriction. The former regimen certainly did not fulfill in their patients the results to be expected from the work of others. They found the very low salt diet difficult to carry out at home. Their work also suggests that salt plays little part in vascular hypertension.

So this matter rests in a debatable position at present with the onus to establish the truth resting upon those who contend that sodium chloride plays an important rôle in the causation of increased arterial tension.

The association of hypertension with increased basal metabolism has been referred to in dealing with hyperthyroidism. From time to time, however, a small series of cases has been reported where it was suggested that hypertension and increased metabolism might occur independently of any disturbance of the thyroid function. This conception was first formulated by Foster (103) who suggested that such patients might form a special group, but he did not altogether exonerate an association with thyroid disturbances. Other writers (Peabody, Meyer and Dubois (104), Aub and Dubois (105), Boothby and Sandiford (106), Boothby and Willius (107), Dameshek (108), Levine (109), Mannaberg (111), Händel (199) and others) have noted the frequent association of hypertension and increased metabolic rate, but have usually considered both conditions due to thyroid disturbance.

Boas and Shapiro (110) have reported five cases with associated hypertension and increased basal metabolism. They believe this constitutes a special syndrome which should be distinguished from the ordinary form of hypertension as well as from thyrotoxicosis. Whether this contention of Boas and Shapiro can be considered as valid has yet to be proven, but the fact remains that there appears to be a close association between increased blood pressure and increased metabolism.

VI. Blood pressure and acute and chronic infections. Many references will be found to the belief that hypertension is a significant sequela of past infections or is associated with chronic septic foci. There are, however, few critical observations which bear directly on this subject. Thayer (112) in 1905 reported the blood pressure estimations in 183 individuals who had had typhoid fever. It would appear from his findings that in these cases there was a relatively increased systolic pressure when compared, according to age decades, with individuals who had not had typhoid fever. Barach (113) found typhoid fever to be the most frequent antecedent infection in cases of hypertension. Swett (159) has remarked on the association of chronic arthritis and

hypertension. He does not attempt to determine the comparative frequency of arterial hypertension and hypertrophic arthritis occurring together in relation to the total number of cases of hypertrophic arthritis. Lemierre and Piédelièvre (119) have reported a case of paroxysmal hypertension during the course of typhoid fever. It would seem however that these cases are rare and are most probably due to some incidental condition quite independent of the infection. These positive results have not been borne out by other observers. Moschowitz (114), Warfield (115) and Ambard (116) have all reported syphilis as being the most common infection while, on the contrary, MacElroy (117) found a history of syphilis in comparatively few of his cases. Walker and O'Hara (118) made an extensive study of the incidence of various infections in individuals with hypertension over 35 years of age, as compared with people of the same age period without hypertension. From their investigations it would seem to be evident that long past infections have a doubtful influence on the development of this functional abnormality. Furthermore, they found a history of syphilis three times as common in their controlled group as in the entire hypertensive group.

From the evidence at hand it would seem difficult to draw any clear-cut association between the occurrence of hypertension and chronic infections. On the other hand, a progressively declining blood pressure may be taken as an index of the severity of an acute infection and its deleterious action upon the vasomotor control. Vaquez (200) reported a large number of cases of acute infections with a preceding hypertension in whom there was a reduction of blood pressure and which in many instances remained at a permanently lower level. From these observations he concluded that the hypertension is primary and independent, at least at first, of any organic lesion.

VII. Hypertension and visceral lesions. The association of vascular hypertrophy, both anatomical and physiological, with visceral disease begins with the classical work of Bright (122) in 1836. His description at that time of the presence of cardiac hypertrophy in renal disease, which he attributed to increased cardiac work, opened a line of investigation which has not yet reached a finality. For many years it was considered that hypertension was practically always the result of renal disease, but with the increased facilities for determining changes in arterial pressure it became evident that this was not the case. More recently it has become obvious that both renal and cardiac lesions may result from an unexplainable hypertension. In consequence, the

clinical significance and interpretation of increased arterial pressure in all its manifestations has fallen into a chaotic condition.

The masterly review by Janeway (123) in 1912 of nephritic hypertension went far to clear away many misconceptions and theoretical conclusions based upon ill-founded hypotheses and we may take his work as a second stepping-stone in the elucidation of this problem.

In order that an understanding of the significance of changes in arterial pressure with visceral lesions may be obtained, and at the same time the association of cause and effect correlated, it is necessary that we deal with them separately. In the preceding sections there has been outlined the different physiological variations and causes of change in arterial pressure. It would be expected that an interpretation of the pathological variations of this function would be subject to similar analysis. Unfortunately, however, it will be found that this is not the case. The reason for the occurrence of changes in arterial pressure are frequently recognisable and therefore such changes may help to elucidate certain abnormal biological processes. In other instances a logical explanation is not forthcoming and, until such can be found, it is fruitless to attempt explanations based upon illogical and falsely conceived premises.

As already stated, Bright was the first to draw attention to one of the complicated pathological complexes with which we are at present dealing. Although he restricted himself to the association of renal and cardiac disease, he did not state that this association was always constant, nor did he venture to speculate beyond certain broad inferences. The most important of these was that hypertrophy of the heart must be attributed to unusual work performed by that organ, and that the cause of the unusual work must lie either in unwonted direct stimulation of the heart or in heightened peripheral resistance. He did not at that time associate with this pathological process the thickening of the walls of the arterial tree, with its consequent decrease of lumen and obliteration of its finer architecture.

During the years following Bright, arteriosclerosis was looked upon as being one of the most important causes of increase in arterial pressure. More recently it has become more and more obvious that unexplained hypertension may in itself not only be a cause of cardiac hypertrophy, but may also produce hypertrophy and fibrosis of the smaller arteries and sclerosis of different organs, the outstanding one of which—after the heart—is the kidney. Here we have, as far as our present knowledge goes, a functional defect leading to gross anatomical lesions. It will be our purpose in the following sections to review,

and as far as possible explain, by known physiological conceptions, the association of variations in arterial pressure with physiological and anatomical abnormalities.

A. Heart. 1. Myocardial lesions: In dealing with the clinical significance of changes of blood pressure in myocardial lesions it is important not to confuse the issues. In the present instance we are considering what myocardial lesions lead to changes in blood pressure, and not what changes in blood pressure lead to myocardial lesions. When there is a primary damage to the myocardium as, for instance, in the acute inflammatory conditions associated with rheumatic fever, chorea, scarlet fever, etc., there is a tendency for the blood pressure to assume a generally lower level than is normal. This may be the result of a compensatory process with lowering of the peripheral resistance in order that the myocardial strain may be lessened. The after-effects of such inflammatory conditions do not in any essential way influence the interarterial pressure unless eventually there be myocardial failure. The same may be said of cardiac vascular lesions. It is claimed that disease of the coronary artery leads to hypertension. This may be true, but only insofar as the coronary lesion is part of a general arterial change. Analogous conditions will be found associated with hypertension when we deal with vascular lesions of the kidneys, brain, pancreas and other parenchymatous organs. It is true that hypertension is frequently associated with angina pectoris but this is more of an accidental association than one of primary cause and effect. Through some undetermined factors, the coronary arteries would appear to suffer more than the arteries of the other organs, hence the symptoms of cardiac embarrassment associated with hypertension. Closely allied to this is the association of bundle branch lesions and arborization block with hypertension. When these lesions are produced by local vascular changes, the latter being but local manifestations of a general procress, there is frequently hypertension, but it cannot be held that the local cardiac lesion is the cause of this. On taking the matter a step further, complete heart block, due to local vascular lesions, may also be associated with hypertension. The literature on this subject was reviewed in 1917 by Musser (124) who found that during the period of heart block the blood pressure was higher than when a normal rhythm was present. The factors governing this increase of blood pressure may be both local and general. It is suggested that on account of the long diastole a large volume of blood is expelled at each ventricular systole. If there is no peripheral lesion it will be found that it is only the systolic

pressure which is increased, the diastolic pressure remaining practically normal if there be no increase of the peripheral resistance.

In disturbances of rhythm, such as auricular fibrillation, flutter, and paroxysmal tachycardia, there is a tendency for the mean blood pressure to decline, even in cases where hypertension had previously existed. Where these disturbances of rhythm occur in cases of unexplainable hypertension, it is probable that the rhythmic disturbance results from a change in the smaller arterial architecture which in itself may be the result of chronic increase in the intervascular pressure.

A somewhat similar process is operative when secondary myocardium failure ensues upon long established increased arterial pressure. Under these circumstances the systolic pressure shows a progressive decline while the diastolic pressure remains more or less constant, thus decreasing the pulse pressure. This is a serious indication of progressive and final circulatory breakdown and it will be found that as the myocardial efficiency is improved, whether by the administration of digitalis or other methods, the systolic pressure and pulse pressure both increase. A lack of increase or a decrease in systolic pressure, on exercise, has been taken by a number of writers as a serious prognostic indication of myocardial failure.

2. Valvular lesions: It may be stated that valvular lesions per se are not associated with any pronounced change in intervascular pressures except where there is a regurgitation through the aortic valves. In such circumstances, the outstanding feature is the increase in pulse pressure. This is generally brought about by an absolute or comparative reduction in the diastolic pressure. It would appear that this is principally due to a reflex dilatation of the peripheral vascular bed producing a lowering of the peripheral resistance. It has been shown experimentally that the characteristic collapsing pulse appears immediately after artificial production of aortic insufficiency: in fact, it may be taken as one of the indications that the experimental procedure has been successful. An increase of the systolic pressure in association with this valvular lesion is not a direct result of the lesion itself but would appear to be produced by a conspicuous compensatory enlargement of the cavity of the left ventricle and hypertrophy of its wall. As a result of this, a larger volume of blood is expelled into the vascular tree at each ventricular systole. This, as in the case of heart block mentioned above, produces a sudden and extreme filling of the vessels, with consequent increase of systolic pressure which is immediately followed by a sudden drop in the inter-arterial tension with a consequent relative and also

absolute reduction in the diastolic pressure. If the diastolic pressure, on the other hand, be increased, it would indicate either a primary or a secondary change in the peripheral resistance.

Analogous changes in blood pressure occur in conditions which lead to a persistent reduction in peripheral pressure and over activity of the cardial vascular system, such as arteriovenous aneurism, patent ductus arteriosus (with left to right shunt), hyperthyroidism, profound anemia, etc.

Relative changes in the arterial tension in different parts of the vascular tree have already been referred to. Such changes were first recognized by Hill and Rowlands (125) who drew attention to the increased pressure in the arteries of the leg as compared to those in the arm in aortic insufficiency, in the recumbent position. This has been corroborated by Leschke (251) and others. That this change in pressure occurs only in association with this lesion, and those analogous to it, has been held open to question by other workers. It may, however, be said that the most conspicuous change occurs in well established cases of this disease.

B. Arterial lesions. It has been stated above how any condition which increases peripheral vascular resistance, such as the injection of adrenalin or pituitrin, leads to an increase of the inter-arterial tension. Another example is to be found in coarctation of the aorta. In this condition there is a stenosis of the aorta which leads to a conspicuous increase of the arterial pressures in the upper limbs, while in the lower limbs the pressure may be so low as to be impossible of estimation. This was first described by Minkowski (126) who reports the case of a young man of 23 years with stenosis of the aorta and a systolic blood pressure in the arm of 300 mm. Hg. Since that time a number of cases have been reported by Moschowitz (148). The diagnostic significance of this difference has not been sufficiently recognized as it is a common finding (127) and occurs only in such cases. The means by which this difference in pressure is produced under such circumstances is easy of understanding. On account of the resistance to the forward flow of blood through the aorta the pressure in the vessels proximal to the obstruction is greatly increased, with an actual reduction in pressure in the vessels distal to it. A somewhat analogous disturbance of the blood pressure occurs in aneurism of the arch of the aorta. If it develops distal to the site of origin of the innominate artery but proximal to that of the left subclavian artery, the pressure in the right arm will be conspicuously greater than that in the left, as the aneurism acts as a buffer.

For many years it was held that arterio-sclerosis of the larger vessels was an important cause of hypertension. Albutt was the first to emphasize the occurrence of conspicuous hypertension independent of sclerosis of the palpable arteries, but few observations have been made upon the relative degree of sclerosis in arteries of different sizes and particularly in correlation with a degree of arterial pressure. The well known picture of arterial changes in retinitis secondary to renal and circulatory diseases has been described by many, but the first reference to a correlation between blood pressure and large and small vessel sclerosis is by Moore (128). He reports 21 patients with aneurism who had an average systolic blood pressure of 141 mm. but found no evidence of disease of the retinal arteries in any case. This was more or less an accidental observation. The question has been more thoroughly investigated by O'Hare and Walker (129) who have made an extensive study of ateriosclerosis with and without hypertension. In 50 cases with obvious sclerosis of the peripheral vessels (radials, brachials and femorals) without hypertension, in only 2 could they class the sclerosis of the retinal vessels as moderate, while in 48 it was slight or questionable. On the contrary, in 50 cases with sclerosis of the peripheral vessels, with hypertension varying from 160 to 266 mm. systolic pressure, there was a moderate to marked sclerosis of the retinal vessels in all. As the authors state, the comparison between these two groups is extraordinary. They pursued the enquiry into those persons who had had a previous history of hypertension but in whom, for one cause or another, the blood pressure had assumed a much lower level, in fact, might be considered to be within normal limits. They give a comparative table showing the previous blood pressure and that existing at the time of the examination of the retinal vessels. This series numbers 16 and in all but two evidence of retinal sclerosis was present. The importance of these findings from the point of view of clinical medicine cannot be overestimated.

It has been shown by Moore (128) that the condition of the retinal vessels is a good guide to the condition of the vessels of the brain and is of value in the prognosis of cerebral complications. Furthermore, it may be taken as a point to differentiate between those cases of arteriosclerosis having a low tension because of cardiac weakness and those in whom hypertension has never existed.

Albutt was so impressed by the occurrence of hypertension without evidence of peripheral sclerosis that he considered these cases as a distinct symptom complex, to which he gave the name of "hyperpiesis."

More recent writers have coined the name "essential hypertension." As this condition occurs independently of any recognisable anatomical change during life, it will be considered under a separate section.

C. Renal lesions: The early recognition of the association of renal lesions with signs of vascular hypertrophy led to a persistent idea that hypertension and nephritis were always associated. But even Bright did not make this claim. That there frequently is a close association cannot be denied but unfortunately the exact reason for it has not yet been elucidated. Janeway in his Harvey lecture reviewed the different theories but could not come to any definite conclusion. It is not our purpose in the present publication to discuss renal function and pathology of nephritis in detail, but merely to refer to them insofar as they may bear any relation to the production of hypertension. As already mentioned, the presence of any pressor substance, such as adrenalin, in the blood of nephritics has never been demonstrated although Ditman and Walker (191) suggested that methyl-guanidine derived from creatine metabolism might be a possible cause of hypertension in advanced renal disease.

The production of hypertension through a decrease of renal substance has always been considered a possibility. As a consequence, a number of workers have attempted to answer this question by removing sufficient renal tissue to induce signs of a reduction of kidney function. On the whole the results have been conflicting. In many instances the methods have been open to question. Pilcher (131) and Anderson (132) were unable to demonstrate any increase of blood pressure after sufficient kidney substance had been removed to produce signs of renal insufficiency. On the contrary, Pazler and Heinike (133) found an average increase in the blood pressure of 21.5 mm., while Janeway (134) by tying off part of the blood supply to the kidney found an increase of between 40 and 50 mm. in the systolic blood pressure. Cash (171) carried out a series of experiments in which he either separated part of the kidney from the main mass or cut off the blood supply. He found an increase of blood pressure (particularly the diastolic) if he left the necrotic tissue in situ, otherwise no change occurred. This increase was maintained for a few days and then returned to the normal level. In order to further test the importance of reduced renal substance and the possible deleterious effects of high protein diet, Anderson (135) carried his experiments in this direction still further but was unable to detect any increase in the arterial pressure. And so, for the present, this matter stands; still awaiting a definite conclusion, although it would

appear from the character of the experiments that an increase of blood pressure does not result from an anatomical reduction of kidney tissue. This is substantiated by the absence of changes in blood pressure in old people where there is a definite reduction of the kidney volume due to senile atrophy as distinct from a contracted or granular kidney. Oppenheimer (173) believes that the increase in blood pressure which may occur with retention of urine is due to a reflex from the bladder as it may be observed when the bladder is empty but in spasm. Further observations are required on this point.

In the course of nephritis there may be considerable variations in the blood pressure. In acute glomerulo-nephritis with anuria a moderate but transitory hypertension occurs. The exact cause of this increase of pressure has not been demonstrated and it would appear to be due to an acute retention of water. As the exudative renal lesion subsides, the arterial tension returns to a practically normal level where it remains in spite of the possible development of edema and other evidences of salt and water retention. In such cases the evidence is against the assumption that excess of sodium chloride is a cause of increased blood pressure.

The progress of the renal lesion from this stage determines the character of the cardio-vascular response. In some cases a lethal result is found without any evidence of associated general circulatory disturbance, while in other cases an apparent arrest of the renal lesion occurs without further disturbance. The more frequent course, however, is a gradual progression of the exudative renal lesion with productive changes and reconstruction of the vascular architecture with fibrosis, thickening of the walls of the smaller arteries and narrowing of their lumen. In other words, the development of the so-called secondary contracted kidney. This process is usually accompanied by serious impairment of the renal function and hypertension. These two functional abnormalities are not necessarily proportionate to each other in chronic renal lesions. It is true that in cases of chronic nephritis, in which there is evidence of nitrogenous retention and failure of urinary concentration, hypertension frequently occurs, but this is not necessarily the case. Hypertension of an order of equal magnitude may develop and become constant, with little or no evidence of interference with renal function. It may be stated, however, that in cases of chronic nephritis in which hypertension develops, there is also occurring in the kidney a definite change in the vascular architecture with thickening and fibrosis of the smaller arteries and decrease in the capillary bed. Why such a comparatively local change in the arterial system should give rise to such a

profound functional disturbance of the circulation is at present not clear. In fact, it remains one of the mysteries of clinical medicine. Krehl (136) has advanced the view that where there is an associated renal sclerosis and hypertension, the two processes are due to a common cause and are not interdependent. In regard to this point it might be well to refer to the close association in lead poisoning and in gout between the paroxysms of chemical disturbance and of hypertension and the subsequently frequent development of profound renal changes. This subject will be further discussed under "hyperpiesis" or "essential hypertension."

In discussing the influence of renal lesions on blood pressure one cannot neglect the occurrence of amyloid disease of this organ. Writers on this subject are in agreement that there is no enlargement of the heart or increase of blood pressure. In fact, in the majority of cases it would appear as if the blood pressure was below normal. Hirose (137) has reviewed the literature and reports 59 cases of amyloid disease of the kidneys associated with chronic nephritis. In all but one of the 15 cases where the blood pressure was recorded it was found to be normal or below. In one case where it was 170 mm. the kidneys were large and the heart was not hypertrophied. In 10 of the 59 cases there was cardiac hypertrophy but in none of these was high arterial lesion noted. The author states that "it appears from this that even if it be assumed that a persistent nephritis produced cardiac hypertrophy and hypertension, the advent of the amyloid-forming process must have reduced the blood pressure to a low point and may even have caused a retrogression in the size of the heart."

It is of interest to note in passing that Miller and Baetjer (152) report seven cases of Bence-Jones proteinuria (discovered accidentally) with hypertension. In only two of these was there any evidence of renal disease. The occurrence of this abnormal proteinuria is unexplainable in at least five of these cases. It brings to mind the necessity of more extended enquiry into the protein content of the urine under disturbed vascular conditions, such as orthostatic albuminuria and the increase of albumin in the urine in cases of exudative nephritis when the upright position is assumed.

D. Nervous lesions. The relation of the pressure in the general arterial circulation and that in the cerebro-spinal system is one of importance. Block and Oppenheimer (153) have compared the systolic blood pressure, the intraspinal pressure and the interocular tension in normal people and in patients suffering from different diseases. They found no

strict parallelism between these three pressures but, apart from local lesions in the eye, if the pressure was high in the arterial system it was likely also to be above the average in the other two and, similarly, an increased tension in the cerebro-spinal system was usually associated with a like increase in the others. Certain exceptions to this general rule were not infrequent. Baillart, Maginal and Saragea (161) found that the ratio between the general arterial diastolic pressure and that in the retinal arteries averages in the normal 1:0.45 but this approaches to unity in arterial hypertension in association with increased cerebro-spinal pressure. If in such cases a small amount of spinal fluid is removed, both of the arterial tensions fall. He suggests that the high pressure in the retinal arteries is due to the high pressure in the cerebro-spinal system. Other observations already reported would strongly suggest the opposite interpretation. Kahler (154) also found in normal people that the systolic blood pressure fell after lumbar puncture. This fall was often considerable. On the other hand, in 29 out of 30 cases of brain tumor, the blood pressure rose after lumbar puncture and sometimes to a considerable extent (in one case by 105 mm.). He discusses this seeming paradox but does not come to any definite conclusions.

In discussing the clinical significance in changes of blood pressure in diseases of the central nervous system, it is well to divide the subject into three parts: 1, lesions affecting the peripheral nerve supply; 2, changes in inter-cranial conditions, and 3, psychic disturbances.

1. Blood pressure in the limbs affected by a chronic hemiplegia usually varies in relation to the spasticity. If the paralysis be of a flaccid type, the blood pressures are usually lower than on the healthy side. If, however, the paralysis be of a spastic character the contrary is usually found. These variations, however, are of a comparatively small order and of little significance.

In transverse lesions of the spinal cord pronounced changes in arterial tension are usually found below the level of the lesion. This subject has been investigated by Miss Yates (155) who found that there was a pronounced fall in the arterial tension below the level of the lesion and recovery occurred if the level of transection did not lie above the level of outflow of the thoracic sympathetic chain. The extent of this recovery depended largely upon the level at which the transection was made and partly upon the length of time allowed for recovery. She found the vasomotor portion of this outfall played the greater rôle in this recovery although it also included the cardio-vascular mechanism in the medulla. When asphyxia was induced after transection, the

asphyxial rise of blood pressure was found to be due to the vasomotor mechanism and this would appear to be operative through the stimulation of the spinal cells or origin of vasomotor fibres by carbon dioxide.

It would appear as if the local increase in blood pressure in peripheral nervous injuries were due more to increased arterial tone than to the increase of the muscular tone, although the two might occur together. On the other hand, in tabes dorsalis where there is a decrease in the muscular tonus, localized increase in blood pressure is reported to occur in those areas which are the site of lightning pains and tabetic crises.

A number of symptoms referable to the cranial nerves, such as tinnitus, headaches, temporary aphasia, double vision, vertigo, nystagmus, etc., are frequently associated with both hypertension and hypotension. It would appear that these are but secondary phenomena, the result of local disturbances of circulation—either from an anemia produced by local spasm of the vessels, or through a general lowering of the vasomotor tone. Such interpretations are merely based upon reasonable presumptions as no definite experimental data are available to elucidate their production.

2. It has long been recognised that increased intercranial pressure produces a conspicuous elevation of the systemic blood pressure. It was for a time debated as to whether this was due to the direct stimulation of the centres in the medulla or the result of general cerebral anemia. Stewart (157) in 1906 described the typical picture as produced by cerebral anemia. Since then this subject has been re-investigated by Roberts (157), Coombs (158) and others. Roberts showed that both the vasomotor and cardio-inhibitory centres are directly stimulated by a slight diminution in their blood supply. He also found that the resulting inhibition checked and sometimes annulled the rise of pressure which vasoconstriction produced. Coombs found on producing bulbar anemia that a maximum increase of blood pressure was reached which was not exceeded when pressor agents acting on the peripheral vascular system were employed.

These observations have an important bearing upon the diagnosis and prognosis of acute inter-cranial injuries, particularly those which encroach upon the cranial cavity or in any manner acutely raise the inter-cranial pressure. Duret (162) has shown by the injection of wax into the cranial cavity that decreasing the inter-cranial space by 5 per cent produced coma, and by 8 per cent resulted in death. Cybulski (164) demonstrated that death is not produced until the inter-cranial pressure equals or exceeds the arterial pressure. The experiments of Cush-

ing (163) indicate that the increase of inter-cranial pressure acts chiefly through a decrease of blood supply to the brain with resulting cerebral anemia. He watched the cortical circulation through a window in the skull during such time as he increased the pressure of the fluid in the inter-cranial space by introducing saline under gravity pressure. He found that the first evidence was a venous stasis, which was then followed by a blanching of the cortex although the veins remained filled. He demonstrated that this anemia was associated with a slowing of the pulse rate and an increase of the systemic blood pressure. When the latter exceeded the inter-cranial pressure then the circulation was re-established. These results were practically identical with those found by interruption of the blood flow through the carotid and vertebral arteries as practised by Roberts and Coombs.

Sieber (165) has made an important study of the relation of increased general arterial pressure and decrease in pulse rate in inter-cranial injuries to the character of the lesion. He came to the conclusion that frequent blood pressure and pulse rate observations not only afforded evidence of the degree of inter-cranial pressure but might be utilised as indications for or against the advisability of relieving the inter-cranial pressure. He also advises that inter-cranial pressure should be relieved before the advanced stage of medullary compression and edema is produced.

It may be taken that in cases suffering from a cranial injury if there be a progressive increase of the systemic blood pressure and a slowing of the pulse rate that an increasing inter-cranial pressure is occurring.

3. Psychic disturbances: On account of the supposed influence of mental agitation on the suprarenal gland, it has been held by some that severe mental perturbation would give rise to a persistent change in blood pressure. This was looked for amongst patients suffering from shell shock, psycho-neurosis and other functional disturbances during the European war, but the evidence in favour of such association was almost negligible. In fact it may be said that in the majority of cases of war exhaustion, and particularly amongst those who occupied positions of great danger and anxiety, that the average blood pressure was apt to decline in association with psychic and physical fatigue. This decrease usually returned to a more normal level after rest. Etienne and Richard (172) have confirmed this point in a group of civilians of all ages who were repeatedly examined during the years of bombardment of Nancy.

A number of studies of blood pressure have been carried out amongst

the insane. In these patients no general rule may be laid down which would indicate that the changes of blood pressure found were directly dependent upon the psychic disturbance. In elderly people the blood pressure is usually found to be elevated, but this was no greater than would be expected in association with complicating physical conditions which are so common in this class of patient.

It is not unusual in cases of insanity with great mental agitation to find an elevated blood pressure. This has been studied by Enebuske (166) who found an increase, particularly in cases of mano-depressive insanity and in dementia precox. In the former type both a systolic and diastolic hypertension occurred during the periods of maniacal exaltation. During these periods it assumed a rather constant level which usually returned to normal as the mano-depressive symptoms subsided. In dementia precox, however, there was a great variability in the vasomotor phenomena during all the period of mental disturbance and over the course of a few days pronounced fluctuations would occur. The exact significance of these vascular changes in insanity cannot be explained. It is suggested by some that both the mental and the vasomotor phenomena are due to a common cause, such as some unknown toxemia. On the other hand, it is suggested that the vasomotor phenomena are the result of the mental perturbation, which produces an exaggeration of the pressor phenomena which ordinarily maintain the inter-arterial pressure.

E. Pelvic lesions. For many years it was considered that a relationship existed between uterine fibroids, myocardium degeneration and hypertension. The exact reasons upon which this opinion was based are not clear. It would seem as if this conclusion were reached more from an impression than from a careful analysis of cases. Heitz (167) reports 17 cases of high blood pressure after hysterectomy for fibroids, in 11 of whom the operation had been done on account of hemorrhages. The most striking feature in his cases was the elevation of blood pressure after the removal of the uterus. It is conceivable that the hemorrhages had something to do with a temporary lowering of the blood pressure before operation. There are, however, no details of prolonged observation before the operation. Also, he did not determine the instance of hypertension occurring in all cases of fibroids of the uterus. Polak, Mittell and MacGrath (168) have published a series of similar cases in whom they found no constant association between such uterine disturbances and cardio-vascular lesions. This was especially definite in young people. It was also evident from their cases that patients

with myomata who had high blood pressure were usually over 40 years of age and were frequently the subjects of renal or cardio-vascular disease. In regard to repeated hemorrhages, they found no direct effect on the blood pressure, but when hemorrhages were suddenly checked, either by operation or by radium, there seemed to be a temporary increase of the systolic pressure which rapidly regained its former level.

It may be stated, therefore, that there is no evidence in favour of the contention that there is a relationship between uterine fibroids and cardio-vascular disease. It has been held by some that increased inter-abdominal pressure due to pelvic growths, either solid or cystic, may so impede the abdominal circulation as to produce a general vascular disturbance. There is nothing to support this contention, particularly when one considers the comparatively small change in inter-arterial tension which occurs during pregnancy. It is quite true that there is a small increase during the latter months of gestation, but it would be more rational to consider this the result of the increased metabolism consequent upon fetal growth than to lay it at the door of a purely mechanical factor.

F. Eclampsia. Quite apart from the consideration of pelvic growths and allied anatomical conditions, there occurs during pregnancy one of the most violent of paroxysmal disturbances of inter-vascular pressure that is known, viz., eclampsia and its allied states. For many years it was considered that there was a close association between chronic renal disease and the toxic complications of pregnancy. It now appears quite clear that this is definitely not the case. It is true that pregnancy, complicated by an acute or chronic renal lesion, may produce an exacerbation of the complicating factor, but the signs, symptoms and chemical disturbances which arise under such conditions are identical with those which would occur in an exacerbation of the renal lesion, provided pregnancy were not present.

The idea that eclampsia was of renal origin was originally based upon the occurrence of albuminuria, and this was further substantiated by the observation that hypertension was also present. With the improvement of laboratory technique and a broader understanding of renal function, it soon became apparent that these two signs were not necessarily indicative of a primary renal lesion. It is not our purpose in the present communication to discuss in detail the pathogenesis of eclampsia, but in order to have a clear conception of the nature of the hypertension which is such an important sign in this disturbance, it is necessary that its relationship to renal disease be reviewed.

A large amount of work has been carried out on this subject by many investigators but probably the most complete has been that accomplished by Stander (185) and his co-workers. There seems no doubt from their work that in eclampsia the urea and base content of the blood are little, if any, disturbed. They found four important deviations from the normal: A reduction in the carbon dioxide combining power of the plasma, and an increase in the uric acid, the lactic acid and the sugar of the blood. They could find no evidence to indicate any interference with renal function per se. It is true that eclampsia may occur in women who already have nephritis, in fact, it would be surprising if such individuals were not to some extent more prone to its development, but carefully analysed figures show that eclampsia is no more frequent in those with preëxisting nephritis than in those with normal kidney function.

The chief characteristic of the blood pressure in eclampsia is the rapidity of the increase, and particularly important is a rising diastolic pressure. In fact, it is taken that a diastolic pressure in a pregnant woman above 95 to 100 is indicative of impending danger. Le Larier (190) goes so far as to state that a rising blood pressure in pregnancy above 120 mm. is a warning of eclampsia and at 150 mm. albumen appears and eclampsia is imminent. This indicates the basis of an interesting and important hypothesis as to the cause of hypertension in this disease and probably, also, the cause of the disease itself. It has already been outlined how the diastolic pressure is an index of the peripheral resistance and when this pressure is increased in comparatively young individuals without signs of sclerosis of the smaller vessels it may be presumed that a contraction of the smaller vessels is present. The hypertension both systolic and diastolic will be in proportion to the severity of the arterial spasm and the rapidity with which it occurs. If this spastic condition of the arteries be sufficiently pronounced, interference with the blood supply to the tissues will ensue. This deprivation would lead, first, to a disturbance in the functional capacity of the organs affected and in time to a definite anatomical change, such as albuminuria in the case of the kidney and fatty degeneration and necrosis in the liver. It has already been pointed out what violent effects may be induced by the production of cerebral anemia. The more important of these in the present instance are vasomotor stimulation, convulsions, coma and death. It is true that bradycardia is not as conspicuous in eclampsia as it is in cerebral anemia, but in eclampsia the arterial spasm is probably not local but affects the cardiac circulation as well and any such interference usually leads to a tachycardia.

The interesting theory of Zangemeister (186) regarding the production of the cerebral symptoms of eclampsia fits into the conception that this disease is primarily one of vascular spasm with the well known development of local edema which occurs in like conditions due to other causes.

If, for the sake of argument, we consider that eclampsia is due to a spasm of the smaller arteries, arterioles, or even the capillaries, thus interfering with the blood supply to many organs and through raising peripheral pressure produces an acute increase of the diastolic and systolic pressure, it is possible to explain practically all the signs and symptoms which occur. The decrease of the CO_2-combining power of the plasma would result from deficient oxidation and increase of lactic acid in the blood. It is interesting to note that these two conditions run parallel and are exaggerated on the occurrence of convulsions. During the convulsions a large quantity of lactic acid would be produced from the glycogen of the muscles. On account of the interference of the blood supply to the tissues the restoration of lactic acid to glycogen is interfered with, and this would lend its influence to a still further reduction of the alkaline reserve. The increase of uric acid in the blood is not so easily explained. As will be pointed out later, this is a common occurrence in other diseases with paroxysmal hypertension. We have already noted the occurrence of hyperglycemia in association with hypertension, but whether this be due to a disturbance of pancreatic or hepatic function, or is produced by an excessive adrenalin action, is not settled. We will have occasion to mention the experiments of Hülse (187) on the presence of a hypothetical substance which increases the sensitivity of the vascular system to adrenalin action.

It would seem, therefore, in eclampsia, that the vascular disturbance is of primary importance and that probably the few chemical disturbances which develop are of a secondary nature. What the cause of hypertension is in these cases is still a mystery. That hypertension is an essential phenomenon in this disease there seems to be no doubt, and any means taken to artificially reduce it, except those with a definite physiological basis, such as absolute rest and the prevention of convulsions with sedatives, would seem to be unwarranted. In view of the pathological lesions which have been found in this condition, the use of anesthetics such as ether and chloroform would seem definitely contraindicated, particularly as these drugs interfere with the reconstruction of lactic acid into glycogen (188).

In addition to the rapid rise of the inter-arterial pressure in eclampsia

there may be, and usually is, an equally rapid decline. In fact, this fall may be so extreme as to produce death. (189). The picture so obtained closely resembles other instances of a cumulative force with a certain degree of compensation but in which the explosion eventually occurs, and the removal of the cumulative force allows the compensatory processes to exercise a malignant influence.

The cessation of the eclamptic symptoms is usually coincident with the termination of the pregnancy although at times the explosion may occur and subside before delivery is produced or after parturition has been completed. This, however, does not necessarily invalidate the theory developed from the hypothesis that it is due to the production or abnormal action of a pressor substance intimately connected with gestation.

G. Miscellaneous. It is not infrequent to find hypertension associated with hemorrhages from different organs as, for instance, epistaxis, hemoptysis, hematemesis, hematuria, etc. These hemorrhages are probably compensatory and are analogous to the excessive bleeding which so frequently occurs from uterine fibromata occurring in cases with hypertension, although in the latter instance the susceptibility to hemorrhage is more pronounced than usual. The importance of these hemorrhages from different viscera is not only to be found in the probable safety-valve rôle which they play, but also because they may lead to a confusion of diagnosis. It should be borne in mind that every case that has hematemesis does not necessarily suffer from a gastric or duodenal ulcer, or other gross anatomical change, and that gastric hemorrhage is produced by hypertension. Of greater importance is the realisation that hemoptysis is a comparatively frequent occurrence in this vascular disturbance. Rossi (174) draws attention to this and warns against ascribing to tuberculosis what is really a hemorrhage from hypertension, and he claims that he has never encountered chronic hypertension in a tuberculous subject.

VIII. Hyperpiesia or essential hypertension. It is to Albutt that the credit must be given for first emphasising the occurrence of hypertension independent of any obvious renal or vascular change. This does not mean that eventually such lesions may not develop, but he clearly defined the fact that hypertension might occur as a definite clinical entity without obvious anatomical change. It must not, however, be confused with conditions in which there may be a definite chemical basis for the change of vascular function such as occurs in gout and lead poisoning. It might be well to define this condition as one in which

there is an increased inter-arterial tension due to an increased peripheral resistance produced by an unknown cause. One of the most distinguishing characteristics of this type of hypertension is the early increase of the diastolic pressure. Although this increase is actually less in amount than the increase of the systolic pressure it is of far greater importance as an indication of the fundamental character of the lesion.

Although it is well to recognize this pathological disturbance of the vascular system when it occurs, it is merely significant as indicating some more fundamental or deep-seated process. It may be taken that there are two schools of thought in regard to the etiology of this disturbance; one, that it is due to an inherent characteristic or susceptibility of the arterial system in certain individuals; the other, that the condition is produced by some pressor substance of unknown character. Although these conditions might seem to be antagonistic they are not necessarily so, and the evidence at hand would seem to indicate that they may be both operative in different degrees in individual cases.

There is an increasing volume of literature in which is outlined the family trees of patients in whom hyperpiesis is of frequent occurrence. Striking instances have been reported by Rosenbloom (176), Wiseman (177) and Nador-Nikitis (178). Raymond (179) was the first to draw particular attention to the occurrence of hypertension and apoplexy as a familial susceptibility. There might be mentioned also Maginal, Heitz, Vakel, Ehrmann and Weiss, who have all contributed, amongst others, certain facts in regard to the familial occurrence of this functional change. Probably Weiss (180) has made the most exhaustive investigation of the subject. He found that there was a large incidence of heart disease and apoplexy as a cause of death in the parents of cases showing essential hypertension and, also, that death occurred earlier in the parents of the young patients with this disturbance. In all of his cases at least one parent had evidence of hypertension, and 50 per cent of the brothers and sisters of all parents of hypertensive cases had died by the age of 55 from hypertension or its complications, or had it before that age. He was also able, he believed, to rule out the influence of both nicotine and alcohol as a causative factor. His findings were so striking as to make him believe that essential hypertension was a constitutional disease with a familial tendency and that the heredity followed the Mendelian laws and was a dominant characteristic.

If this presumed hereditary characteristic should have any basis in fact, one would expect that a fairly large number of young people would show evidence of this vascular disturbance early in life. This has been

borne out by the findings of Alvarez (181) and Diehl and Sutherland (182). Alvarez, when examining young men in the second draft for the United States Army, was impressed by the large number of them who were subject to hypertension. This led him to a more extensive investigation of the subject and he came to the conclusion that in women before the menopause the blood pressure was remarkably constant and hypertension seldom appeared, while after 35 the curve began to resemble that of the male sex in whom he found hypertension to be fairly common and subject to unexplainable fluctuations. These results were substantiated by Diehl and Sutherland, who based their results upon the examination of 5,122 male students of the University of Minnesota, with repeated examinations over a period of three years, and found that 9 per cent of them had a systolic blood pressure of over 140, and 0.5 per cent over 160. Their final analysis revealed the fact that 2.8 per cent of these students had intermittent hypertension; 5.4 per cent a transient one, and that 1.6 per cent of the entire group showed a persistent increase in the inter-arterial pressure. Also they considered that there was strong evidence in favour of an association between overweight and hypertension; Alvarez, on the other hand, strongly argued for an hereditary diathesis.

Hahn (183) puts forward the contention that vaso-neuroses are common in children of parents with hypertension and believes that chronic hypertension is an adult form of vaso-neurosis. Morelli (184) draws attention to the quantitative increase of vascular spasm which occurs in different people when their arteries are irritated by external stimuli, and he found this spasm to be particularly severe in cases of hypertension or those descending from so-called hypertensive families. O'Hare (224) investigated this subject and found that the vasomotor system in vascular hypertension was extremely labile and sensitive. Rest or exercise produced a conspicuous and abrupt rise. That the arteries of all individuals do not respond in a similar manner is quite evident to those who have had a large experience in arterial puncture. In all cases when the artery is pricked by the needle there is at least a local spasm, and this is more pronounced when the smaller arteries, as the radials, are irritated, in comparison with the larger ones such as the brachial and femoral. In a fairly large number of people the spasm does not remain local but extends to a greater or less degree through the whole vascular tree. One often encounters extreme cases in whom the irritation of the artery locally produces a sudden spasm of the whole arterial system, leading to a disappearance of the pulse in the extremi-

ties; a great increase in the inter-arterial pressure in the larger vessels where it may be detected; bradycardia, syncope, unconsciousness and sometimes a picture which closely resembles death. Any who have had the opportunity to observe such a crisis cannot but be struck by its similarity to the effect of a toxic dose of adrenalin. In what manner these individuals differ from their fellows it is difficult to say, but those who believe in the hereditary irritability of the arterial system will point to this as an inherited characteristic.

We now come to deal with what evidence there is to indicate that hyperpiesis is caused by a pressor substance. This might be either a normal constituent of the body produced in an excessive amount, or in normal amount, operating upon a susceptible vascular system, or, it may be a substance resulting from abnormal metabolism which is being produced through some metabolic perversion, or from a deviation of the normal metabolic cycle.

Guanidine. In 1909 Ditman and Walker (191) advanced the theory that many of the symptoms in nephritis, eclampsia and allied disorders were due to the poor oxidation of certain nitrogenous bodies, especially those resulting from creatine metabolism. As the result of this deficient oxidation they believed that relatively large quantities of creatinine, methyl guanidine and guanidine were produced, and they put forward experimental and chemical evidence to demonstrate how methyl guanidine, etc., might be produced. They also pointed out the pressor action of these toxic bodies. Boyd (130) in 1916 again called attention to the possibility of methyl guanidine exerting a toxic influence in nephritis and other conditions with hypertension. This subject was re-investigated by Major and his colleagues in 1924. Major and Stephenson (194) demonstrated that the intravenous injection of methyl guanidine produced a prolonged rise in blood pressure and, in a later communication, they showed that not only methyl guanidine, but also guanidine and dimethyl guanidine produced a similar reaction. They found that this increase in inter-arterial tension could be counteracted by calcium or potassium chloride. There does not seem to be any doubt that guanidine compounds do exert a pressor influence. Major showed (195) that there was a decrease in the amount of guanidine substances in the urine in cases of hypertension, whether it was associated with disease of the kidneys or not.[1] He further demonstrated that as the blood pressure goes down the guanidine excretion increases (196) but, in the

[1] Major and Weber have found an increase of methylguanidine in the blood of cases of hypertension. (Bull. Johns Hopkins Hosp., 1927, xl, 85.)

end, he does not commit himself as to whether hypertension is caused by an increased production of guanidine, due to an error of metabolism or due to a faulty excretion of guanidines by a damaged kidney. This is further emphasized by Howard and Rabinovitch (198) who brought forward some evidence to confirm Major's work, but they raised some important points which must be elucidated before a definite correlation can be established. They sound a warning against premature conclusions in this regard.

Uric acid. The intimate association of gout and primary contracted kidney has long been recognised but there are but few cases recorded where blood pressure readings have been taken during the course of acute and paroxysmal gout. This is probably to be explained by the rapid decline in the occurrence of this lesion with its typical manifestations during the past 30 years. In 1918 Rosenbloom (201) reported 4 typical cases of paroxysmal gout in whom he had records of the blood pressure during two or more attacks. In the acute exacerbation there was a pronounced increase in both the systolic and diastolic pressure. In each instance the systolic pressure increased to over 200 mm. and in one case it increased from 110 mm. during the remissions to 240 mm., and the diastolic from 70 to 120 mm. Unfortunately he did not record any observations on the uric acid content of the blood. Such paroxysms of increased arterial pressure are very suggestive of those which we have already mentioned as occurring in eclampsia, where there is practically always an increase of the uric acid in the plasma but no other obvious disturbance of nitrogenous metabolism.

Degrez and D'Orleans (202) have shown that the intravenous injection of uric acid produces a prolonged increase in the systolic blood pressure. The association of hyperuricemia and hypertension has been frequently noted, but it has usually been accounted for by a deficiency in nitrogenous excretion by the kidney, due to a chronic renal lesion. Fishberg (203) has shown that in essential hypertension there may be a high content of uric acid in the blood without any urea retention. The cases reported by him give no evidence of renal insufficiency and the most common cause of death was cerebral hemorrhage: he also noted the frequent association of diabetes mellitus. Kylin (204) has also pointed out the frequent association of hypertension, hyperuricemia and hyperglycemia.

In addition to guanidine and uric acid, Vaquez (205) has drawn attention to the paroxysmal increase of blood pressure which occurs in lead poisoning and draws a parallelism between such an increase and that

which occurs in eclampsia. This is of interest, as the other classical etiological factor in primary contracted kidney is lead poisoning. Vaquez claims that one can trace the course of lead poisoning with the sphygmomanometer and can foretell imminent encephalopathy when the pressure rises.

Cholesterol. Cholesterol is another product of metabolism which has been considered as a possible etiological factor in the production of hypertension.[2] Fahr (245), Van Leersum (246), Schmidtmann (250) and Schönheimer (247) have all reported an increase of blood pressure in rabbits occurring with the arterio-sclerosis following the prolonged feeding of cholesterol in oil, or of substances rich in cholesterol. There appears to be no doubt as to the production of the arterio-sclerosis but there is a doubt as to the value of the blood pressure readings. Shapiro and Seicof (248) confirmed the production of the arterio-sclerosis but could not substantiate the increase in blood pressure. The main difficulty in such experiments is the uncertainty that the methods of determining the blood pressure give consistent results. Until such a method is proven to be exact the results must be accepted with reserve. The method of Shapiro and Seicof would appear to be the most exact and should give the more consistent results.

Maliwa (254) determined the protein, the cholesterol and the bilirubin concentration in the first and last portions of blood from a venesection (350 to 500 cc.). He claims to have found three groups of changes and hopes that he may be able by these to make possible fine distinctions in the differential diagnosis of hypertension. In what way he does not state. Westphall (206) claims that he found hypercholesteremia present in 71 per cent of his patients with essential hypertension, and attempted the experimental production of arterial hypertension by cholesterol feeding in rabbits. As yet, his attempts are far from conclusive although he has attempted, and apparently with some success, to use his theoretical conclusions as a basis for therapeutic measures. The weakness of his hypothesis is to be found in the fact that hypercholesteremia is present in many conditions in which there is no hypertension, and he brings into play many other accessory factors upon which hypercholesteremia is dependent in its theoretic production of hypertension.

Adrenalin. In a previous section there has been taken up the ques-

[2] Cashin and Moravek have found that the intravenous injection of cholesterol produces amongst other results a primary fall and secondary and prolonged elevation. (Amer. Journ. Physiol., in press.)

tion as to whether adrenalin exerts an important action in maintaining the normal blood pressure. The balance of proof would seem to indicate that a decision in this matter is still to come. The fact that the intravenous injection of this substance produces in experimental animals the profound vasoconstriction, with consequent elevation of the inter-arterial pressure and slowing of the cardiac rate, led to the hypothesis that in otherwise unexplainable hypertension and hypotension that either an excess, or deficiency, or perversion of the suprarenal excretion was the underlying cause of this functional disturbance. Högler (252) contends that normal human plasma inhibits the peristalsis of a cat's intestine by the Dittler method, while the plasma of cases of hypertension has a stronger action and that from cases of Addison's disease has no effect. Bröking and Trendelenburg (207) and Stewart (208) were unable to demonstrate adrenalin in the blood of cases with hypertension. In spite of this, many have clung to the theory that otherwise unexplained changes in blood pressure are to be found in disturbances of the suprarenal gland.

Closely allied to this theory is one based upon the hypothesis that in cases of hypertension the vascular system is more sensitive to the action of adrenalin. Clough (192) investigated the relative reactions in individuals with hypertension as compared with normals and found that he obtained a pronounced response to the injection of 1 mgm. of adrenalin in 68 per cent of the cases of hypertension as compared with 18 per cent of normal individuals. This was corroborated by O'Hare (224) and by Jansen (225). Two theories might be advanced to explain such reactions; either that the vascular system is inherently more susceptible to the action of adrenalin, or that some unknown substance in the blood of patients with hypertension enhanced its action. The experiments of Hülse (187) would suggest the latter. He found, in animals, a much more pronounced response to adrenalin injected after 3 cc. of nephritic serum had been introduced into the blood stream as compared to a similar amount of normal serum. This point must be further investigated before this theory can be accepted as Lehmann (253) found that changes in blood pressure after adrenalin injection were no gauge as to the tonus of the autonomic nervous system.

Many experiments have been undertaken in the hope of being able to demonstrate the presence of a pressor substance in the plasma in cases of hypertension. These attempts have usually been carried out by injecting into a normal animal a certain quantity of blood obtained from cases with increased inter-arterial pressure. A complicating factor has been

the occurrence of anaphylactic phenomena. Gheorghian and Niculescu (212) claim to have demonstrated the presence of a pressor substance in the blood of patients with hypertension by injecting a small quantity of the serum into the ear vein of a rabbit. Danzer, Brodie and Miles (209), taking precautions to prevent anaphylaxis, came to the conclusion that there is present in the blood of cases with hypertension a pressor substance which has an influence somewhat similar to that of adrenalin. As yet, their results have not been confirmed.

Amines. It is well known that certain amines, such as tyramine and histamine, when injected into the blood stream might either elevate, as in the case of the first, or reduce, as in the case of the second, the systemic blood pressure. These substances can be obtained from putrefactive digestion. Histamine has been demonstrated as being present in the contents of the cecum in apparently normal individuals (210). It is true that it has been found in infinitesimal amounts (211). If one amine is found in the bowel it has been presumed that others might be formed also by the splitting off of carbon dioxide by the so-called carboxylase bacteria before deamidation.

In view of these observations it has been claimed by some that disturbances of blood pressure are dependent upon abnormal function of the bowel and attention has mainly been focused upon so-called intestinal stasis. That this condition with its possible abnormal digestion may produce disturbance of the vascular function is still purely hypothetical and awaits definite proof.

Organ extracts. In 1895 Oliver and Schafer (213) found that extracts of the thyroid gland, spleen, parotid and sub-maxillary glands had a marked depressor effect. Since that time many workers have obtained substances with a similar action from many organs. In a number of the earlier experiments there is no doubt that the depressor effects of these extracts were confused with the now well known anaphylactic shock. On the other hand, there seems no doubt that many of these bodies exert an influence of a different character. In recent years attention has been particularly directed towards the effects of liver extracts upon the systemic blood pressure. Roger (214) in 1921 and 1922 obtained liver extracts, some fractions of which had a pressor action while other fractions produced a depressor effect. He also found that extracts of kidney tissue had similar effects. The most recent work has been carried on by Major (215) MacDonald (216) and James and Laughton (217) and their co-workers. They all claim to have produced a fraction of liver extract which reduces blood pressure. Some of the reports

deal with hypertension artificially produced in rabbits with guanidine and these workers find that the extracts act in a manner seemingly different from that of histamine or choline, although some of the charts published by MacDonald would strongly suggest that the reaction obtained was similar to that of histamine, and MacDonald acknowledged that his extract contained histamine in relatively large quantities. On the other hand, Major (219) and James, Laughton and MacCallum (218) claim that their extracts were proven, both biologically and chemically, free of histamine.

The clinical reports on cases of hypertension so far published makes one agree with Major, that "definite conclusions can only be drawn after a large number of patients have been treated over a long period of time. The evidence at the present time that the liver extract is effective in certain cases of arterial hypertension is very suggestive, but not conclusive."

It would seem from the works published in the last thirty years as if the extracts of many organs had a more or less similar effect. Whether this be due to a common factor, or each tissue has individual characteristics of its own, is not at all clear. It must not be forgotten that the results in the earlier experiments may have been due to anaphylactic phenomena and, in the light of our present knowledge, it would be well if the experiments with other tissue extracts were repeated.

Kidney. The historical and pathological association of diseases of the kidney and hypertension have already been mentioned. Probably on account of this there is a persistent endeavour to lay the cause of hyperpiesia at the door of some renal lesion. It is held by many that sclerosis of the smaller arteries is more pronounced in the kidney than it is in other organs in essential hypertension, this frequently being so without any other obvious change, either functional or pathological, in the kidney itself. That the kidney produces any specific substance which has a direct effect on the vascular system is doubtful, nor is there evidence to indicate that tissue extracts of the kidney have any specific action either in raising or lowering the vascular tension. Petrovsky (255) reports some interesting experiments in which he found by perfusing a kidney with Ringer-Locke solution that the perfusate contained a substance which exerted a pressor action on the systemic vessels and augmented the cardiac action. He could not claim that this was specific for the kidney as he found a somewhat similar effect produced by perfusates of other organs. The substance is thermostable and passes through a Berkefeld-Kerzen filter.

Some have claimed that hypertension is due to the initiation of a vascular spasm in the vessels of the kidney, from which it spreads to the other organs. Theories like this, based upon a modicum of suggestive evidence, have not so far been amenable to experimental proof.

Blood. It has been claimed that one of the possible theoretical causes for an increase of arterial tension was to be found in the increase of viscosity of the blood. Lyon (221) has made an exhaustive study of the relationship of blood viscosity to blood pressure and has come to the conclusion that there is no relationship between these two conditions. Adams and Brown (222) have found in cases of essential hypertension that the hemoglobin values were normal, or above, but that in cases with renal insufficiency an anemia developed. It would seem, therefore, from their figures, that changes of blood pressure, per se, are not dependent upon any blood disturbance.

Some workers have claimed that in subjects with hypotension the blood platelets were increased, while in subjects with hypertension the contrary was found. Roskam and Brull (223) report somewhat similar findings but do not claim that this is a consistent relationship and suggest that the blood changes are secondary to the changes in vascular tension, particularly as the latter may affect the contents of the abdominal viscera either through emptying a large quantity of blood into the circulation, or by having a contrary influence.

IX. Hypotension.[3] As hypertension should be considered as an indication of abnormal function at one end of the scale, so must hypotension be considered as indicating functional derangement at the other end. Hypotension is usually used to signify a lowering of the systolic pressure below a certain level, but it must not be forgotten that coincident with this there is a reduction also in the diastolic pressure.

It has already been pointed out that the normal range of blood pressure is based upon the average healthy individual, but all investigations of large numbers of people have revealed the fact that there are wide divergences from the average normal which occur in otherwise apparently healthy individuals. When the systolic pressure is below 110 mm. Hg hypotension is usually considered to exist. Barach (226) found this to be present in about 3.5 per cent of normal people. He points out that it usually occurs in the hyposthenic or asthenic type of individual. These are underweight, have long, poorly developed chests and frequently present a visceroptotic configuration. Roberts (240)

[3] Friedlander has recently published a monograph on "Hypotension" which covers the subject in a most exhaustive manner. (Medicine, 1927, vi, 145.)

has made a detailed study of a large series of cases with hypotension and came to the conclusion that there is less evidence of cardiac derangement in cases with low blood pressure than in those with a so-called normal tension or with hypertension. Furthermore he found it frequently to be present when no signs or symptoms could be detected referable to it.

In a previous section reference has been made to the changes in blood pressure in different positions and how the tension was usually lower in the upright position in the hyposthenic type of individual. Such people are apt to have a progressive decline of blood pressure on standing and may have syncopal attacks on exercise, but more particularly on standing still, as on sentry duty, or when suddenly assuming the upright attitude (242). This condition has been compared by Hill to the hutch rabbit which loses consciousness when held by the ears. Reference has already been made to the physical differences which usually exist between those who habitually have a blood pressure on the higher limits of normal and those in whom the opposite occurs.

There would seem to be a congenital or hereditary tendency toward low arterial tension, but this has not been stressed as much as in the case of hypertension, probably because the consequences are not so spectacular, alarming or dangerous. Frost (249) has found the hypertension and longevity were in an inverse ratio. He also found that hypertension was associated with a definite increase in mortality directly proportionate to the degree of the pressure elevation and this mortality was very largely due to the development of circulatory and renal disease. Hypotension after 50 was usually indicative, other things being equal, of longevity and freedom from cardio-renal lesions.

The symptoms accompanying hypotension are usually headache, transitory vertigo and easy mental and physical exhaustion. Any combination of these may be present, and on account of their indefiniteness do not, as a rule, present a very concrete clinical picture. The factors underlying the production of this chronic state of lowered arterial tension are less understood than those producing hypertension. Its association with chronic infections, particularly tuberculosis, has been recognised for many years but the exact cause of this association has never been explained, unless it be due to myocardial insufficiency. It has been claimed by some that it is due to a "suprarenal insufficiency" due to a generalized toxemia. For this there is absolutely no proof. It has been pointed out that arterial hypotension does not necessarily occur even when the adrenalin output is completely cut off. It has

been stated that in acute infections such as pneumonia, influenza and the acute exanthemata, there is usually a lowering of the blood pressure. The method whereby this is produced is unknown. That it does occur there is no doubt, although at no time during the course of an ordinary infection does it assume significant proportions. On the other hand, it may develop to an alarming degree, particularly during the terminal stages of acute diseases when the condition of the patient closely resembles that found in secondary shock.

The factors which are known to reduce blood pressure may be summarised as follows:

1. A sudden decrease in the circulating blood volume.
2. A pronounced lowering of the peripheral resistance through dilatation of the capillaries whereby an adequate amount of the circulating blood may be prevented from returning to the heart, and
3. Through myocardial insufficiency.

Hemorrhage. The constant association of lowering of the blood pressure with hemorrhage is one of the best-known clinical observations. It is true it does not occur with equal severity in all individuals under any given loss of blood, nor is the rapidity of this loss a constant criterion of the subsequent disturbance of circulation. It may be taken as a general rule that the more copious the hemorrhage and the more sudden it be, the more pronounced will be the resulting hypotension. There seems to be no doubt that this disturbance of circulatory function is the direct result of the loss of circulating blood volume. The arterial pressure may be restored to some degree by the introduction into the circulation of a fluid, such as normal saline. But in addition to loss of fluid volume there is also a loss of colloids, an important one of which is the hemoglobin. The hemoglobin, along with the other colloids, can be restored by means of transfusion, but if this be not possible, the introduction of pure gum solution (227) in some form (228) is more efficacious than physiological saline alone. It is evident from such experiments both on animals and on man that the primary cause of hypotension in hemorrhage is due to the loss of blood volume. A somewhat analogous condition is found in cholera, where an extremely low blood pressure occurs as a result of the great loss of fluids through the bowel, with consequent reduction of the blood volume with blood concentration.

Shock. Anaphylactic shock: Heidenhain (229) first produced a pronounced lowering of the blood pressure by intravenous injection of peptone. This was associated with marked concentration of the blood. Pearce and Eisenbrey (230) demonstrated the similarity between the

fall of blood pressure in peptone intoxication and that in anaphylactic shock, although the fall under the latter conditions was much more persistent than under the former. They also found a great engorgement of the vessels in the splanchnic area and a concentration of the blood. This pronounced fall in blood pressure may not only be immediate but sometimes occurs six or more days after an injection of serum and coincident with other signs of delayed serum sickness (241).

Dale and Laidlaw (231) first drew attention to the decline of blood pressure after the injection of minute doses of histamine. Dale and his co-workers continued to investigate this problem and demonstrated that they could produce a typical form of shock. They found that the histamine produced a dilatation of the capillaries with apparent damage to their walls and an escape of fluid either into the tissue spaces or into the surrounding cells themselves, thus bringing about a concentration of the blood with a reduction in blood volume and subsequent decrease of the amount of blood returning to the right heart. The relation of histamine shock to the conditions that exist in anaphylaxis, the terminal stages of infections and in surgical shock, is one of great interest.

Traumatic shock. It is not the intention in the present communication to deal with traumatic shock in a detailed manner[4] but only insofar as it is necessary to explain the cause and significance of the lowered blood pressure. Shock is usually found in cases of severe traumatic injury and may or may not be complicated by hemorrhage.

Shock has been classified by Cowell (235) as primary wound shock and secondary wound shock, while Quénu (236) divided it into immediate, primary and secondary. It would appear that time and hemorrhage are the two factors which determine the difference between these conditions. If the hemorrhage be acute and severe, as from the injury of one of the larger arteries, all the symptoms of acute blood loss as already described will develop. If hemorrhage does not occur, or is moderate at the time of injury, the symptoms of shock do not, as a rule, develop immediately. In 1905 Malcolm (233) claimed that shock was due to a pronounced constriction of the peripheral circulation thus preventing an adequate amount of blood being circulated with a resultant apparently low peripheral blood pressure. He described a condition which he believed was due to peripheral stimulation of the arteries,

[4] Those interested in the subject of shock are referred to the monograph by Connor—*Traumatic Shock*, New York, 1923, and the Reports of Shock Committee, Medical Research Council, London, numbers 25, 26 and 27 (1919), for a full discussion of shock in its various aspects.

which would appear to be analogous to that which has been described above as occurring in some people during the process of arterial puncture. The symptoms appear immediately after injury and personal idiosyncrasy to vascular trauma seems to have an important bearing on its development. It has been pointed out by Santy (232) and also by Archibald and MacLean (234) that this immediate shock does not necessarily bear any relation to the severity of the initial injury and is a comparatively rare condition. Patients may recover from this type of shock and some hours later secondary or delayed phenomena may occur. This condition would appear to be entirely different from that which occurs immediately after trauma and is closely analogous to that found in histamine poisoning.

The whole question of shock has been carefully reviewed and numerous experiments have been recorded by Cannon (237) in his monograph on this subject. He states that "the theory of secondary shock, which has the strongest support both in clinical observations and in laboratory experiments, is that of a toxic factor operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the tissues." Many of the signs and symptoms of shock can be explained on this basis. Probably the most important of these is the reduction in blood pressure and the consequent inadequate supply of oxygenated blood to the tissues. The decreased supply of oxygen and the coincident change of the pH of the blood and of the tissues themselves soon exert a profound and irretrievable damage, particularly to those highly organized systems which are most sensitive to these changes. As this acute hypotension is so easily recognised its clinical significance is great, not only in diagnosis but also in prognosis. A systolic blood pressure below 60 mm. is practically always followed by death.

Anesthesia. The question of the lowering of blood pressure and many of the other signs of shock which occur after surgical operations is of great practical importance. There is no evidence to indicate that this is essentially different from that which occurs after other traumatic conditions. The symptoms are most usually those of secondary shock, but occasionally they simulate the characteristics of primary shock. Dale (239) has shown that animals under anesthetics are much more sensitive to minute doses of histamine than are those without an anesthetic. It is suggested that other factors may play a rôle in this question. It has been shown by Stander (185) that there is a pronounced accumulation of lactic acid in the blood during anesthesia and particularly

if there is any anoxemia. Long (238) has found that anesthetics interfere with the restoration of lactic acid into glycogen in skeletal muscles after the glycogen has been reduced through exercise, while Long and Brow (188) have demonstrated a conspicuous reduction in the glycogen content of the myocardium after general anesthesia. Whether postoperative shock has altogether the same etiology as secondary traumatic shock remains to be definitely demonstrated. The known factors, however, are very suggestive that their etiology may rest on a more or less common basis. There seems no doubt that the disastrous consequences are produced by a common disturbance of circulation, of which reduction in blood pressure is the most conspicuous sign.

Myocardial insufficiency. Myocardial insufficiency may result from either developmental, degenerative or inflammatory processes which do not necessarily include valvular lesions or congenital defects of the septa, etc. Probably the most definite type of developmental myocardial insufficiency is to be found in cases of so-called status lymphaticus. Symmers (243) found that 50 per cent of such cases that came to autopsy had abnormally small hearts and that in 40 per cent the aorta was hypoplastic. There was no evidence adduced to indicate that the heart muscle or large vessels were otherwise diseased. It would appear that the hypotension found in such cases was due to an inherent defect in volume rather than of structure. In other words, that the engine was not big enough for the machine.

In acquired myocardial insufficiency the cause is entirely different. In such cases the volume of the heart and aorta may not only be normal in size but in fact is usually greater than normal. The best examples are to be found in chronic anemia, wasting diseases, coronary infarction, chronic rheumatic and syphilitic myocarditis, etc. Under such conditions there is a definite reduction in the contractile power of the heart. The defect is central and not peripheral as this term is usually employed. The association of a low systolic pressure (and usually a small pulse pressure) with other signs of myocardial embarrassment, such as precordial pain and pulsus alternans, is of grave moment. Navarro (244) has emphasized the gravity of the combination of hypotension with pulsus alternans. Furthermore, the idea that hypertension is a necessary concomitant to angina pectoris should be discarded, as hypotension with anginal symptoms usually indicates a progressive circulatory failure, particularly if there is evidence of a previous hypertension having been present.

X. Pulse pressure. Sufficient attention is not, as a rule, paid to the

significance of changes of pulse pressure. Stone (257) has described it as the "kinetic" force which keeps the blood in motion, and it is therefore an important indication of the efficiency of the circulation. Warfield (256), and others, have repeatedly drawn attention to the importance of variations in pulse pressure. As it is the difference between the systolic and diastolic pressures it indicates the amount of force which the left ventricle exerts on the arterial system, over and above the resistance present during ventricular diastole. Other things being equal, the pulse pressure should give a fair indication of the volume of blood which is being expelled into the aorta and larger vessels at each systole. Experimental evidence would indicate that this is roughly the case. With an increase of the diastolic pressure there is a progressive increase of the pulse pressure and, therefore, of the systolic pressure. If it be taken that the average ratio between the diastolic and systolic pressures is as 80 is to 120, then the pulse pressure would be 40. With an increase of diastolic pressure to 110 one would expect to find the systolic pressure to be 190 to 200, or an increase of the pulse pressure to 80 or 90, or approximately 100 per cent. It could not be taken, however, that the volume of blood expelled into the aorta at each systole had also increased 100 per cent. If that were so, with a resting pulse pressure of 120 the increase of the systolic output should be as 200 per cent of the normal. This we know is not the case but what the exact ratio between pulse pressure and cardiac output may be has not as yet been determined.

The anatomical and clinical results of increased pulse pressure have been summarised by Warfield (256) to be *1*, increase in the size of the cavity of the left ventricle; *2*, permanent increase in the diameter of the arch of the aorta; *3*, if the pulse pressure be over 70 mm. there is an increase in the size of the large distributing arteries, and *4*, bronchial breathing on auscultation over the lower half of the manubrium.

An increase of pulse pressure does not necessarily signify an increased strain on the arterial tree, although it would undoubtedly seem to indicate an increased burden on the myocardium. For instance, in cases of aortic insufficiency, arterio-venous aneurysm or hyperthyroidism, where there is a low diastolic pressure and a normal or increased systolic pressure, the pulse pressure is usually greatly exaggerated. Under these circumstances any secondary consequences are usually to be found in the heart itself rather than in the blood vessels.

In cases where there is a persistent increase of the systolic blood pressure, a gradual decline of this with maintenance of the diastolic pressure signifies gradual failure of the myocardial function. The same signifi-

cance is not to be attached, however, to a declining pulse pressure with an also declining diastolic pressure. It would seem quite definite that as the peripheral resistance becomes less the pulse pressure also is reduced and still maintains an efficient circulation.

It is held by many that a persistent pulse pressure of under 30 mm. will not allow of an adequate circulation. This is undoubtedly the case when the diastolic pressure is normal or above but the same importance cannot be attached to a small pulse pressure when the systolic and diastolic pressures are below normal. A declining pulse pressure is of much more importance when there is a relatively high diastolic pressure than when hypotension is present. The importance of careful and repeated readings of the diastolic and systolic pressure in all cases of cardio-vascular disease cannot be over-emphasised. Of particular importance is the correlation of these repeated readings so as to make a composite picture of the progress of the case and not a number of isolated and unrelated observations.

XI. Causes and consequences. It has been stated that variations in blood pressure are to be considered as indices of changes in the circulatory system. It has been shown how such variations are necessarily part of the ordinary daily life and development of the individual and as such must be considered normal phenomena. It is when they assume an abnormality independent of such requirements that a pathological condition may be assumed to exist.

Reference has frequently been made to "spasm" of the peripheral vessels. It would seem reasonable to suppose that this term could be applied in the acute paroxysms of hypertension found in gout, lead poisoning, eclampsia and tabetic crises. Also it might be justified to use this term in the artificial hypertension produced by adrenalin or guanidine. But it is not reasonable to take for granted that spasm of the vessels is the whole process underlying chronic hypertension of renal disease and hyperpiesia. Up to the present time the study of the arteriole and capillary pressures in human disease has not progressed far enough for the exact location and manner of this so-called "spasm" of the peripheral vessels to be located.

The histo-pathological changes occurring with a persistent hypertension may now be briefly summarised. The initial lesion is apparently to be found in the capillaries and arterioles where a hyaline swelling and fusion of the cells of their walls occur. This is produced quite independently of the blood pressure and would appear to be the cause of the changed vascular function. It is also quite distinct from the ordinary

atheromatous changes in the arteriosclerosis of the larger vessels. As the lesion in the capillaries and arterioles proceeds, the vascular bed becomes reduced. This vascular reduction is well seen in the afferent and efferent glomerular vessels in the kidney. It is, however, a general phenomenon and influences the finer vessels in all areas more or less equally. As the lesion progresses the peripheral resistance increases and gradually the increasing arterial tension exerts its influence on the larger vessels. The intima of these becomes thickened with fibrous tissue and the muscular coat becomes hypertrophied. The palpable arteries then acquire a tougher or more rubbery character on palpation. Atheromatous ulceration with calcification does not usually occur.

As a consequence of the increase of fibrous tissue and hypertrophy of the muscle a narrowing of the lumen results. The burden of this change falls upon the smaller arteries, many of which through this process may be obliterated, leading to a reconstruction of the vascular architecture. This still further diminishes the vascular bed and leads to a reduction of the blood supply to the tissues with progressive disturbances of *structure* and of *function*. Evidences of progressive depreciation of function are usually to be found in the kidney, heart, brain, pancreas and other parenchymatous organs as well as the skeletal muscles. Another important result of the hyaline cellular swelling and fusion of the cells of the smallest vessels is a general weakening of their walls. This is indicated by the tendency to hemorrhages which occurs if the pressure is maintained. Examples of this are to be found in the retina, brain, kidney, lungs and many other organs.

The factors that determine which organ shall manifest the greatest interference with function are not known. But upon this interference depends the development of the symptoms which dominate the final clinical picture and lead to the death of the individual. In this deviation of final manifestations lies much of the confusion in regard to this disease. The eventual functional consequences are more or less accidental, the primary and all important pathological cause is in the peripheral vascular system and the treatment of the results is but symptomatic. So also is the treatment of the symptom of hypertension itself. This problem will not be solved until the etiological factors are known and prevented or removed.

Chronic hypotension as a rule does not lead to the same disastrous consequences as does hypertension. If it be sudden, as in shock, and the systolic pressure rapidly declines to 60 mm. or less, death will occur from want of sufficient blood being supplied to the vital organs. In

chronic diseases where there is a progressive lowering of the blood pressure this should be looked upon as a general decline of all bodily functions and should not be considered as a condition apart.

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